HANFORD THYROID DISEASE STUDY
FINAL REPORT

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This revision of the HTDS Final Report corrects the reference numbering, typographical and formatting errors, and the numbers in Table IX.G-4. In addition Figure IX.Q-22, which was inadvertently missing from the original report, has been added.

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V. FIELD PROCEDURES AND METHODS, RESULTS OF DATA COLLECTION PROCESS

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Executive Summary

I. Background

The Hanford Thyroid Disease Study (HTDS) was mandated by an act of Congress in 1988. The Centers for Disease Control and Prevention (CDC) was directed by Senate Bill 2889 to conduct a study of thyroid morbidity among persons who lived near the Hanford Nuclear Site between 1944 and 1957. A team of investigators at the Fred Hutchinson Cancer Research Center (FHCRC) and the University of Washington in Seattle was selected by the CDC to conduct the study, and a contract was awarded to the FHCRC on September 19, 1989.

The primary purpose of the study was to determine whether thyroid morbidity is increased among persons exposed to releases of radioactive iodine from the Hanford Nuclear Site between 1944 and 1957. The study was also designed to further determine in what way any increase in thyroid morbidity was related to the dose of radiation received (i.e., the characteristics of any dose-response relationship). Secondary objectives of the study included the following: 1) to determine whether hyperparathyroidism is increased among persons exposed to the Hanford radiation and, if so, to determine in what way the increase is related to the dose of radiation received; 2) to provide information to residents of the communities surrounding the Hanford Site regarding the objectives, design, and conduct of the study, as well as the findings and results of the research; and 3) to assess the appropriateness of the methods employed and the degree to which such an investigation could be successfully planned and executed, given the long interval since exposure and the uncertainties regarding radiation dose.

This study was conducted as a follow-up prevalence study. That is, a group of individuals (a "cohort") was selected on the basis of presumed past exposure to varying levels of radioactive iodine (^{131}I in particular) released into the atmosphere from Hanford, based on place and year of birth. Individuals in the cohort were located and those who participated had a dose estimate calculated from answers to a dosimetry questionnaire, and were examined for the presence or history of thyroid disease. The primary analyses focused on living participants who received medical examinations to detect thyroid disease, and for whom thyroid radiation doses were estimated using the dosimetry system developed by the Hanford Environmental Dose Reconstruction (HEDR) Project. All forms of thyroid disease were investigated as part of the study and were included in the analysis, as were abnormalities of the thyroid gland seen on ultrasound examinations. In addition, primary hyperparathyroidism was evaluated by screening individuals for hypercalcemia.

The work was conducted in two stages. The first was a Pilot Study, the primary purpose of which was to evaluate the feasibility of the methods proposed, and to develop the specific operational procedures and data collection instruments needed for a full study. The second stage was to implement the remaining fieldwork to complete such a study. This approach allowed the accumulation of information and experience prior to initiation of the more costly full-scale study.

The Pilot Study was completed in December 1994, with a report issued January 24, 1995. Reviews of the Pilot Study by the National Research Council's Board of Radiation Effects Research of the Commission on Life Sciences and the federal Advisory Committee for the HTDS concluded that a full-scale epidemiologic study should be undertaken. The fieldwork for the Full Study was completed in December 1997. This document summarizes the Final Report of the Hanford Thyroid Disease Study.

II. Fieldwork

A. Cohort Definition and Participant Selection

To achieve the primary objective of the study, it was important to identify a cohort that would provide the greatest likelihood of detecting an association between Hanford radiation exposure and thyroid disease, if such a relationship exists. This was accomplished by defining a cohort that would include adequate numbers of people with the highest possible radiation doses to the thyroid from Hanford, as well as people with very low radiation doses to the thyroid from Hanford.

Extensive efforts were made to investigate different sources of information that could be used to construct a cohort of people who might have been exposed. Ideally, such a list would include everyone in a relatively large population living in the region around the Hanford site during the time period that atmospheric releases of radioactive iodine occurred, and would contain enough identifying information on each person to allow them to be located for the study (several decades after exposure). Only birth records provided a viable unbiased source for identifying a cohort.

For the purposes of participant selection only, residence at time of birth was considered a surrogate for the anticipated radiation dose to the thyroid from Hanford, since doses could only be estimated from data collected during the study. To select study participants for the Pilot Study, a birth roster was constructed based on all births to mothers resident in the Washington State counties of Benton, Franklin, Walla Walla, Okanogan, Ferry, and Stevens. Following the Pilot Study, and based on the dose estimates for Pilot Study participants, Adams County was added for the Full Study selections, in order to maximize the numbers of participants with high doses. Adequate numbers of participants with no or very low dose were obtained in the Pilot Study selections from Stevens, Ferry, and Okanogan counties, and no further selections were made from these areas.

Preliminary estimates from the HEDR project suggested that the highest thyroid doses were likely to be in people exposed as infants or children during the first years of Hanford operations. This is because infants and children receive higher thyroid doses per unit exposure, due primarily to the small size of their thyroid glands. Existing literature also suggests that the risks radiation-induced thyroid disease (and possibly hyperparathyroidism) are greatest among those exposed at youngest ages. For these reasons, the Pilot Study included people born from 1942-46, since the large majority of atmospheric releases of radioactive iodine from the Hanford facility occurred in 1944-46. For the Full Study, additional selections from the years 1940 and 1941 in Benton, Franklin, and Adams counties were included to maximize the number of potentially high dose participants. Thus, the cohort contained people with exposure beginning as early as the prenatal period, and as late as age three. An additional benefit of choosing a young group was that mothers and close relatives of participants born during 1940-46 were more likely be alive and available for interview, compared to those of persons born earlier.

Selection of potential participants from the Birth Roster was stratified by geographical area, year of birth, and sex. The purpose of stratification by geographical area and birth year was to assure that adequate numbers of high dose and low dose participants were identified, so that as wide a range of doses as possible was obtained. Stratification by sex also reduced the possibility of confounding by sex that could reduce the efficiency of the study. Geographical areas were defined to distinguish predominantly rural areas from those that are predominantly urban, because residents of predominantly rural areas may have been more likely to consume fresh raw milk than their more urban counterparts. A total of 5199 individuals were selected to form the cohort.

B. Tracing and Locating Study Participants

Because members of the study cohort were identified solely on the basis of birth records from the mid-1940s, extensive effort was required to locate them as adults nearly fifty years later. Thus, the primary objective of the tracing component of the study was to identify a current address and telephone number for all living cohort members, so they could be recruited to participate in the study. A second objective was to obtain confirmation of death, as well as date and cause of death, for all those who were deceased.

Several approaches were used to trace potential participants. Initially, relatively easy to use and readily accessible sources were used. Subsequently, more resource-intensive and costly resources were employed to find the more difficult to locate individuals. A final attempt to locate the most difficult to find potential participants was made by using established professional locating services and military locating services.

Of the 5199 cohort members, 4350 living individuals were located and 527 individuals were confirmed deceased. Thus, nearly 94% of the cohort was located, with their identities confirmed. Only 322 potential participants (6.2%) remained "unable to locate" at the end of the study. Notably, the ability to locate well over 90% of all potential participants did not vary substantially by sex, or geographic region of birth, or year of birth. Almost 84% of all potential participants were located as living, and their identities (whether they agreed to participate or not) were confirmed directly by contact with the potential participants themselves or with close relatives who could verify their identities and current addresses.

Five hundred twenty-seven (10.1%) of the cohort members were confirmed to be deceased by a close relative and/or other reliable source (such as death certificate). The proportion confirmed deceased was higher among males (12.7%) than females (7.5%). Sixteen potential participants (0.3%) were located as living, but died during the study prior to completing a clinic. Death certificates were obtained for 93% of the total 543 deceased.

At least one living cohort member was located in every state in the U.S. except for Rhode Island. Fifty-four percent of those located resided in Washington State, 9.4% in California, 9.1% in Oregon and 2.7% in Idaho. The only other state where more than 2% of the living cohort members resided was Texas (2.2%). Thirty-six participants (0.8% of those located) lived in countries outside of the U.S., including Canada, Dubai, Ecuador, Germany, Mexico, Saudi Arabia, South Africa, South Korea, England, Guam, Australia, Japan, France, Saipan, Hungary, Columbia, and Taiwan.

C. Recruiting Study Participants

The objectives of the recruiting effort were to contact living cohort members, obtain their agreement to participate in the study, and to identify an appropriate respondent to complete the Computer Assisted Telephone Interview (CATI). Once a potential participant was located through the tracing procedure, initial contact was made by mail. In some instances a preliminary letter or phone call was necessary to confirm the potential participant's identity. Each living potential participant located received an initial contact letter, fact sheet, and a description of what participation in the study would entail.

A recruiter called each located potential participant five to seven days after the first contact letter was mailed. A minimum of 10-15 evening attempts were made at various weeknight and weekend time periods, and a minimum of three daytime (weekend and weekday) calls were attempted. If the potential participant could not be contacted by phone after 20-25 attempts, a second letter was sent explaining that the study had been unable to reach them at the phone number on file, and asking them to call the toll-free HTDS number. After 40-45 attempts resulting in no contact with either the potential participant or a household member, the potential participant was considered “unable to contact” and no further attempts were made.

If a potential participant refused, the recruiter asked him/her to complete a Refusal/Demographic Questionnaire. Twelve demographic questions relating to race, ethnic origin, income, religion, and education level were asked in order to obtain a general profile of those who refused to participate, or who withdrew after initially agreeing to participate. The recruiter also completed a Refusal Assessment after the call to record the nature and strength of the refusal from the recruiter's perspective.

A total of 4239 potential participants (97.4% of all living, located cohort members) were contacted by telephone and invited to participate in the study. An additional 93 (2.1% of all living, located cohort members) were located to an address, and were sent one or more letters, but could not be contacted by telephone. Of those contacted by telephone, 3564 (84.1%, or 81.9% of all located, living cohort members) agreed to participate in the study. Of those located alive, 634 (14.6%) refused to participate.

Willingness to participate did not differ substantially by sex, year of birth, or geographic region of birth. "Not interested" and/or "no time" were by far the most commonly given reasons given refusals, accounting for 64.8% of all refusals. The second most commonly cited reasons were "illness" and "impairment" (7.6%). An additional 41 potential participants were determined to be unable to fully participate during the recruiting process and were consequently not included in the study regardless of willingness to participate.

D. Computer Assisted Telephone Interview

The primary objective of the Computer-Assisted Telephone Interview (CATI) was to collect information that would be used as input for calculating an estimated radiation dose to the thyroid gland for each study participant. A CATI was conducted by an interviewer who read the interview text and questions from a computer screen, and recorded the responses as they were given.

The CATI was designed to collect information from the early years of the participants' lives, including time *in utero* if necessary, from 1944 to 1957. The interview was "location-driven" so that the information collected was specific to locations and periods of time directly relevant to the atmospheric releases of ^{131}I from Hanford. The following topic areas were included in the CATI interview: 1) general demographic characteristics of the participant and his or her family; 2) a residential history of the participant from birth through 1957, and for the mother while pregnant with or breastfeeding the participant; 3) sources of the milk consumed by the participant from birth through 1957, and by the participant's mother while pregnant and breastfeeding the participant; 4) milk consumption patterns of the participant from birth through 1957, and of the mother during pregnancy and breastfeeding; and 5) other patterns of food consumption, including green and leafy vegetables, fruit, and free range chicken eggs by the participant from birth through 1957, and by the mother while pregnant and breastfeeding. In addition, medical history information was obtained for both the mother and the participant, including the following: 1) thyroid diseases and selected other medical conditions diagnosed and treated in the participant; and 2) history of medical radiation exposures, either diagnostic or therapeutic, for the participant, and for the mother during pregnancy and breastfeeding.

To help the CATI respondents accurately report detailed information about their child (or sibling) from very long ago, several elements of the cognitive approach to interviewing were incorporated into the design of the CATI. The key element to this approach is to mentally take the respondent back to the time period in question, and have them remember as much about that time as possible. As more memories of the time in question are recalled by the respondent, the likelihood of remembering answers to specific questions increases.

Memory materials were developed to help the respondent prepare for answering the interview questions. Background information was provided to encourage memory about specific topics. The memory

materials were organized into a booklet that was sent with a Residence History Questionnaire to respondents in advance of the interview. In addition, the text of the interview was refined to include references to specific parts of the memory materials at key points during the interview.

Of the 2712 participants who identified a CATI respondent, interviews were completed for 2266 (83.6%). Of the 3447 eligible study participants who completed the clinic, 2133 (61.9%) had a CATI interview. In 29 instances, CATI interviewers determined the quality of the data provided by respondents was too poor to be considered reliable. Expanded interviews were performed at the clinic for these 29 participants.

E. Scheduling

The primary objective of the scheduling activity was to provide each participant with at least three options for clinic attendance, with the least possible inconvenience to the participant. A schedule of clinic dates and locations was developed based on the current residences of participants. Clinics were held in Seattle, Pasco, Spokane, Walla Walla, Yakima, Wenatchee, Colville, Omak, Portland Oregon and Vancouver Washington. Most participants from outside Washington State attended clinics in Seattle.

Multiple attempts were made to contact all participants, and every participant was offered several options for clinic dates. Each scheduled participant was sent a letter that included: 1) the date and time of clinic appointment; 2) location of clinic and directions; 3) travel arrangements summary and/or tickets (if applicable); and 4) Interview Preparation Worksheet. If a participant canceled a clinic appointment, an attempt was made to reschedule the participant. A participant who canceled a clinic appointment would be rescheduled an unlimited number of times. If a participant decided not to participate in the study during the scheduling process, the scheduler assessed the reason for the withdrawal and addressed the participant's concerns in an attempt to retain participation. If the participant persisted in the withdrawal, she or he was asked to complete a Refusal Questionnaire.

Approximately 90% of those who initially agreed to participate completed a clinic. The number of participants who withdrew after initially agreeing to participate was 298 (7.7%).

F. Clinical Evaluation

The objective of the clinical component of the study was to provide a thorough clinical examination of each study participant to determine the presence of thyroid disease, or primary hyperparathyroidism. Each participant was administered an In-Person Interview prior to the clinic examinations; this is described in more detail below. Following the interview, each participant underwent a full complement of examinations to determine the presence or absence of any thyroid disease or primary hyperparathyroidism. The examinations included thyroid ultrasound, independent thyroid palpation by two study physicians, and blood tests for thyroid and parathyroid function, and anti-thyroid immune response. Additional studies were requested if indicated by the presence of palpable thyroid nodules.

The physical examination was conducted separately by two study physicians. The results of their examinations were reviewed, and if there was any disagreement, the two examiners conferred and re-examined the participant together to reach a consensus. The findings of each physician were recorded separately, as were the findings of any consensus examination, prior to review of the ultrasound scan. If abnormalities were found on the ultrasound which were not found on physical exam, the two physicians performed a final consensus examination. The physical examination and ultrasound findings were then discussed with the participant.

Participants found to have discrete, palpable, solitary thyroid nodules or dominant nodules within a multinodular gland upon examination were asked to undergo fine-needle aspiration (FNA) biopsy of the nodule. Participants who wanted to delay the procedure could either return to the HTDS clinic site on another clinic date, or have the FNA performed by a local physician in their community. Thyroid nuclear scans were recommended for participants whose examination and laboratory results were suspicious for the presence of autonomously functioning thyroid nodules, Graves Disease, or toxic thyroid nodules.

A total of 3447 eligible participants were examined in the HTDS clinics. Of the 3447 participants, 3439 (99.8%) had blood drawn for thyroid function studies, and 3446 had thyroid ultrasound. Of the 272 participants for whom FNA was recommended, 259 (95.2%) underwent the procedure, while 28 of the 29 (96.6%) participants recommended to have a nuclear scan complied.

G. In-Person Interview

The purpose of the In-Person Interview was to obtain information directly from the study participant about his/her past exposures to occupational and/or medical irradiation, history of thyroid disease, and general demographic information. In addition, for those participants who could not identify a respondent for the dosimetry interview, an expanded version of the In-Person Interview provided details regarding residence history and limited information on the type of milk consumed, for use in estimating their thyroid radiation doses from Hanford's atmospheric releases of ^{131}I. The In-Person Interview was conducted before the participant began the medical components of the clinic (ultrasound, blood draw, and physical examination). This was done to ensure that the participant's responses could not be influenced by knowledge of examination results. All interviews were conducted in person by trained, experienced interviewers.

The In-Person Interview included questions about the participant from age 15 to the present, in the following topic areas: 1) general demographic characteristics; 2) residential history, including dates and locations of residences, 3) occupational history, focusing on occupations and industries with potential of exposure to any form of ionizing radiation; 4) military history as obtained in both the residential and occupational sections, especially regarding possible exposures to nuclear weapons tests (e.g., in Nevada or the Marshall Islands); 5) medical history, including dates and places for all thyroid-related diseases and symptoms; 6) history of medical and dental X-ray exposures; 7) history of nuclear medicine procedures; 8) history of radiation therapy; 9) selected lifestyle factors, such as patterns of tobacco use; and 10) familiarity/bias questions to assess knowledge of the Hanford releases and any strongly-held beliefs about their possible health effects.

All 3447 eligible participants attending a HTDS clinic completed an In-Person Interview. Six interviews were judged to have insufficient residence history information to calculate a dose estimate. One participant was unable to complete the interview because of developmental disabilities, however the participant's father (who was unable due to illness to participate in a CATI dosimetry interview) was mailed a modified version of the expanded In-Person Interview questionnaire and provided the information in this manner. Overall, 61% of participants completed the Standard In-Person Interview, while 39% completed the Expanded version.

H. Clinic Medical Review and Final Diagnosis Determination

The objectives of the Clinic Medical Review and Final Diagnosis Determination processes were to: 1) evaluate each participant's clinical thyroid examination results from the HTDS clinic visit; 2) communicate clinic results to participants in a timely manner and, when indicated, to the participant's health care provider; and 3) assign the final diagnoses for each case, according to the format developed using all information available prior to and including the HTDS clinic.

Following each clinic, results of the laboratory tests performed on blood specimens, of radiologists' reviews of ultrasound examinations, and of the study pathologist's evaluation of any FNA specimens were received in the HTDS office within 5-6 days. Physicians reviewed each participant's clinic results, and a letter informing the participant of the results was sent. A Final Diagnosis Determination Form was completed for all remaining participants. All participants received their clinic results within 3-4 weeks following their clinic appointment. Letters were also sent to each participant's health care provider, if the participant indicated this was to be done.

If follow-up tests were recommended to a participant, that participant's clinic and follow-up results were reviewed at another Clinic Medical Review once the results were received in the HTDS office. A second results letter was mailed to the participant and their health care provider, describing the results of the follow-up tests. The Final Diagnosis Determination Form was then completed.

All 3447 eligible participants who attended a study clinic received a Clinic Medical Review. Eighty percent of participants had a Final Diagnosis Determination Form completed at the time of their Clinic Medical Review. The remaining 20% had either historical medical records or post-clinic recommendations for further diagnostic procedures, and had a Final Diagnosis Determination Form completed following compilation and review of the records from those providers.

A total of 259 participants had FNA procedures performed at the clinic or on the recommendation of the HTDS physicians. Of these, 47 were recommended at Clinic Medical Review to have further biopsy or surgical procedures to rule out a diagnosis of thyroid neoplasm. In addition, 29 participants with thyroid nodules or suppressed TSH were recommended to undergo thyroid nuclear scan. Twenty participants had an abnormal calcium level and were recommended to have additional blood drawn for parathyroid hormone (PTH) studies to confirm or rule out a diagnosis of hyperparathyroidism. Thirty participants were requested to have additional blood drawn due to abnormal or borderline thyroid function.

I. Historical and Post-Clinic Medical Records Review

The primary objectives of the medical record component were to: 1) document thyroid problems reported by study participants and CATI respondents; 2) obtain any cytological or histological specimens from previous biopsies or surgeries for review by the study's pathologist; and 3) obtain the results (including histological specimens) of any further diagnostic or surgical procedures recommended by the HTDS as a result of a finding at the HTDS clinic. A secondary objective of the medical record component was to obtain cause of death information on all deceased cohort members, in order to assign cause of death codes and perform a mortality analysis.

During the CATI interview, respondents were asked to provide the names (and addresses, if known) of any physician who saw the participant for diagnosis or treatment of thyroid disease. At the time of the In-Person Interview, the participant was asked to provide the names and addresses of physicians or institutions where they had been diagnosed or treated for thyroid or parathyroid disease, and to sign a consent form for the release of information from each of these providers.

For each deceased cohort member, the death certificate or informant information was used to complete a Cause of Death Form. In addition, the primary cause of death was coded using the ICD9-CM system. For those whose date of death preceded the use of the ICD9-CM system, the primary cause of death was also back-coded using the system in use at the time of death.

Reports of historical medical records were obtained for 694 participants, with a total of 1259 consent forms completed to obtain medical records from different providers. While the majority of reports were made during the In-Person Interview, CATI Interviews yielded 30 of these reports.

Of the 1259 Medical Record Consents obtained, a total of 795 (63.1%) separate medical records were received by the HTDS. No records were received for 464 requests (36.9%). In 102 (8.1%) cases, records could not be requested because the physician was deceased or retired, or a current address could not be identified. For 128 (10.2%) requests, records were unavailable due to the destruction of records, the inability of the provider to identify the patient, or an inability to locate the records. In 232 (18.4%) cases, records were not received after several contacts, without explanation as to why they were not available.

Of the 694 participants identifying historical medical records to be requested, pathology or cytology slides were requested for 52 (7.5%). In a few cases, more than one set of slides was requested, for a total of 58 separate requests. A total of 42 sets of historical pathology or cytology slides were received for 42 (80.8% of slides requested) participants.

One potential concern is that diagnoses of disease outcomes might be missed when requested medical records or slides could not be obtained: none or only part of the requested records or slides were received for 199 (29%) and 160 (23%), respectively, of the 694 participants for whom such requests were made. However, even if a medical record or slide could not be obtained, the likelihood of a missed diagnosis was generally low because in most such situations the HTDS evaluation provided a definitive assessment of whether the diagnosis for which the medical record was sought was confirmed or not confirmed.

Medical records documenting further diagnostic studies recommended as a result of the HTDS clinic findings were requested for 35 participants, with a total of 72 separate requests. All but one of these records were obtained, with at least one record obtained for each of the 35 participants. Thirty-three of these participants also had histology or cytology slides requested, for a total of 35 separate requests. All 35 of these specimens were obtained.

Death certificates were received for 504 of the 543 deceased cohort members. Cause of death was coded for 543 deceased cohort members.

J. Dose Estimation

The primary analyses of dose-response relationships were based on individual estimates of radiation dose to the thyroid from Hanford's atmospheric releases of ^{131}I, specifically organ doses to the thyroid that were estimated from data collected during the CATI and/or the Expanded In-Person Interview. The CIDER program developed by the HEDR Project was used to calculate estimated doses. In particular the CIDER output for an individual consisted of 100 realizations of the estimated cumulative total organ dose to the thyroid from ^{131}I.

Each of the 100 realizations of dose was calculated for a fixed set of conditions regarding the source term, environmental transport, and uptake of ^{131}I, and these conditions for a given realization were the same for every participant. The 100 realizations were obtained by randomly varying the conditions, i.e., the uncertain parameters in the HEDR models for source term, transport, etc., in order to characterize the uncertainty in the resulting dose estimates. Thus it is useful to view each realization as consisting of a set of doses, one for each in-area participant. For many purposes it was useful to have a single number or

"point estimate" to represent each participant's dose. For each living evaluable in-area participant, the median of the 100 realizations of dose, $d_i = \text{median}(D_{i,1}, \ldots, D_{i,100})$ for participant i, was used as a summary measure of that participant's dose. .

Of the 3447 eligible participants who attended a study clinic, 3440 were considered evaluable for the study, i.e., had sufficient information for dose estimation and could be adequately examined for thyroid disease. The CIDER program calculated estimates of doses accumulated by people while living within a 75,000 square mile geographical domain around Hanford. Dose estimates could therefore be calculated by the CIDER program for 3191 of the evaluable participants who lived within that domain at least some time from the start of Hanford operations in 1944 through the end of 1957; these 3191 are designated "in area" participants. The remaining 249 "out-of-area" participants did not, according to their CATI or Expanded In-Person Interview data, live within the domain during that time period. Although the CIDER could not calculate dose estimates for the out-of-area participants, they were included in the study.

K. Data Management

The primary objective of the Data Management Plan was to specify the procedures to develop and maintain the study databases, and the procedures that would be used to ensure data quality. Principal components of the plan included duplicate entry for all data forms, range checks encoded in the data entry programs, and consistency check programs run on the data after entry. A second objective of the Data Management Plan was to maintain the confidentiality of the data. This included data in computerized form through the use of passwords and control of limited access to directories and data files, and to paper records, which were stored in locked files in locked offices or in a file room which had limited access via keycard.

In order to ensure high data quality, all data entered from paper forms were subject to double-entry verification. Additional computer programs were written to check and crosscheck all of the data, both within a data form and across data forms. For example, the diagnoses coded on the Final Diagnosis Determination Forms were compared to all the other data collected (i.e., examination forms, ultrasound forms, CATI data, In-Person Interview data, and the tracking system) to ensure that all appropriate diagnoses were included. All inconsistencies were investigated by review of the participant's records, including audiotapes of CATI interviews when necessary. Once any changes were made to a database, check programs were run to ensure all changes had been made correctly.

L. Data Quality Control

In addition to the data management plans and procedures outlined above, additional steps were taken after data collection to ensure a high degree of data quality. These efforts included 1) more extensive between-table consistency checks of the In-Person Interview data and the CATI data, 2) hand calculation of the participant's diet portion of the CIDER input data files ("scenario files") for 10% of those with a CATI, 3) comparison of the mother's diet portion of the scenario file for all those with a CATI based on a separate computer program written by a programmer other than the one who created the scenario file program, 4) comparison of dose estimates produced by a CDC programmer versus those produced by HTDS, and 5) review by a second programmer of complex analysis programs that included code other than standard SAS procedures.

III. Special Considerations

A. Coordination with the Advisory Committee

In June of 1990, an Advisory Committee was appointed by the Secretary of the Department of Health and Human Services to advise and consult with the CDC regarding the design and conduct of the study. The committee was established pursuant to the *Federal Advisory Committee Act, (5 U.S.C. Appendix 12)*. The role of the committee was to review the development of the study protocol and conduct of the Pilot Study, assist in determining the feasibility and design of a full-scale epidemiologic study, and advise CDC on the analysis of the study results.

Initially, meetings of the committee were to be held on a quarterly basis in Atlanta, Georgia. In recognition of the interest in the Pacific Northwest in such proceedings, however, the committee asked that at least one meeting per year be held in Washington State. Following completion of the Pilot Study, meeting frequency was reduced to approximately once per year, with the majority of these held in Seattle, Washington.

Meetings of the Advisory Committee were open to the public. All materials presented to the committee became public record, with copies available for members of the public at the meetings. Meetings held in Washington State were nearly always accompanied by an evening Public Meeting to allow members of the public to attend and to ask questions or make comments regarding the study.

Each meeting of the Advisory Committee began with an update on the progress of the study since the previous meeting. These presentations included the status of preparations for the study field work, or later, the numbers of study participants completing each phase of the study. Updates on the separate work concerning Native American populations were also included. Requests for further information from the committee were documented, and information provided by study staff and investigators, as necessary.

B. Public Involvement

An important aspect of the HTDS was the provision of prompt, accurate, and complete information to the public. In this context it was crucial that contacts be established with members of the populations most interested in the work. Interested parties included representatives of the States of Washington, Oregon, and Idaho; the Native American Tribes and Nations in the study areas, and local area residents.

The public information activities of the study were designed to accomplish the following goals: 1) to assure that residents of the region understood the issues that led to the initiation of the study, the purpose and objectives of the study, its basic epidemiologic design, and the time schedule within which it was to be conducted; 2) to provide opportunities for the public to express concerns and comments regarding the design and conduct of the study, and to answer public questions regarding all aspects of the project; 3) to create public interest and support for the study, particularly in ways that such support might enhance participation by persons selected to be study participants; and 4) to assure broad dissemination and proper interpretation of final study results.

Throughout the study, and particularly in the early phases, the study investigators participated in public meetings held during the bi-monthly meetings of the HEDR Technical Steering Panel (TSP), and contributed to the planning activities of the Communications subcommittee of the TSP. The HTDS also supplied the TSP with a fact sheet that was included with TSP fact sheet mailings. This written material was updated periodically as the study progressed.

Several separate approaches were also taken to provide information to the public regarding the HTDS. Initially, the study protocol was made available for public review and comment prior to its submission to the CDC and the Advisory Committee. In conjunction with this activity, a series of public meetings were held throughout the Northwest to discuss the protocol with the public and to answer specific questions.

In addition to the study fact sheet mentioned above, several study brochures were developed and a newsletter describing the progress and status of the study was initiated. The brochures included the following: 1) HTDS Fact Sheet; 2) Questions and Answers about the Study; 3) Questions and Answers about Radiation and Thyroid Disease; and 4) Review of Thyroid Disease and Approach to Diagnosis. A master mailing list, which included the lists previously maintained by the FHCRC, the CDC, and the HEDR Project, was assembled to mail the newsletter and brochures to interested individuals. By the later stages of the HTDS, the mailing list contained nearly 9700 names. Early in the study, the newsletter was published on a quarterly basis. Following the Pilot Study, however, yearly updates were used to inform interested parties of the study's progress. A total of 15 issues were published. A special issue summarizing the findings in the Draft Final Report was distributed in January 1999.

Finally, study investigators and staff have been available to answer questions on a regular basis. A phone line was designated in the Seattle study office for public inquiries, and a toll-free telephone number was established at the Fred Hutchinson Cancer Research Center for the Hanford Thyroid Disease Study (1-800-638-HTDS). People selected as study participants, and members of the general public, were encouraged to use the toll-free number to contact the study office if they had questions or scheduling conflicts. As access to the World Wide Web became more common, a web site for the study was established at the FHCRC. All study brochures and newsletters have been available at that site since January 1997, and are updated as necessary.

C. Native American Component

Nine Native American tribes and nations have reservations and ceded lands in the region around Hanford: Colville, Couer d'Alene, Kalispell, Kootenai, Nez Perce, Spokane, Umatilla, Warm Springs, and Yakama. Members of these tribes and nations were exposed to ^{131}I from Hanford, and the original congressional mandate that led to the HTDS called specifically for the inclusion of "Indian tribes and tribal organizations." The approach taken in the HTDS regarding the Native American populations was determined by two important characteristics of those populations. First, the lifestyles of many Native Americans were quite different in many respects from those of the non-Native population. In particular, many Native Americans followed traditional cultural practices, especially regarding diet and sources of foods, which might influence the doses they received from Hanford's ^{131}I, but which were not explicitly modeled in the CIDER program. Moreover many Native Americans maintained a seasonal migratory pattern of residence. Second, because the tribes and nations have sovereign rights recognized by the United States, conduct of a research project such as HTDS would require the approval and active cooperation of each tribal government. Thus, the objective of the HTDS with respect to the Native American populations was to assess the feasibility of conducting a study to determine whether thyroid disease has increased among Native Americans exposed to atmospheric releases of ^{131}I from Hanford.

Sample size and power calculations were carried out to determine whether it would be feasible to conduct a retrospective cohort study using individual dose estimates, similar to that being conducted for the HTDS Full Study. These calculations were based on data provided by eight of the nine tribes regarding tribal-specific lifestyle and dietary practices. These data are likely to more accurately account for lifestyle patterns and practices specific to each tribe than using assumptions derived from the non-Native American population, and therefore the representative dose estimates are likely to more accurately approximate the doses members of each tribe would have likely received from Hanford. Similarly, the demographic data provided by each tribe are likely to more accurately reflect the size and demographic makeup of each tribe around the time of the Hanford releases.

Even under very liberal assumptions regarding the number of tribal members who might be available to participate in a study, and the thyroid radiation doses Native Americans received from Hanford's atmospheric releases of ^{131}I, a study nearly twice the size of the HTDS Full Study (6426 living evaluable participants) would have only 50% power to detect an effect of the magnitude targeted by the Full Study, i.e., a 5% increase in total thyroid neoplasia per Gray. Even under a more extreme assumption that the baseline probabilities for thyroid neoplasia are only half of those assumed in the HTDS Full Study, a study of 6426 living evaluable participants would only have 71% power to detect the same magnitude of effect. Thus, it was recommended that a study of the design of the HTDS full study would not be feasible in the Native American population encompassed by the nine tribes in the Hanford region.

IV. Statistical Methods

In the primary dose-response analyses, the exposure for each living evaluable in-area participant was represented by the estimated radiation dose to the thyroid from Hanford's atmospheric releases of ^{131}I, as calculated using the CIDER program created by the HEDR Project. The primary dose-response analyses for disease outcomes and ultrasound-detected abnormalities (UDAs) of the thyroid were based on regression models in which the probability of having the outcome of interest varies as a linear function of estimated thyroid dose, specifically the median dose as mentioned above. The model for this primary analysis permitted the background probability of the outcome to depend on sex, but assumed a common regression coefficient (slope) for the dose-response. The regression coefficient can be interpreted as the change in the probability of the disease outcome, per unit change in dose. Since the purpose of the study was to determine whether thyroid disease has been increased, significance testing focused on the null hypothesis that the probability of having the outcome of interest does not vary with dose (i.e., that the regression parameter has value zero) and the one-sided alternative hypothesis that the probability increases with increasing dose (i.e., that the regression parameter is greater than zero). Alternative sex-stratified dose-response models were also considered, specifically linear-quadratic and logistic models.

Identification and analysis of confounding and effect modifying factors was accomplished through the analysis of generalizations of the logistic exposure-response models. For disease outcomes, these generalizations allowed the background probabilities of the outcome of interest (i.e., the intercept parameters) and/or the regression parameters to vary as functions of a number of factors that might potentially confound the relationship between thyroid radiation dose and the outcome of interest. The influence of uncertainty of the dose estimates on the dose-response relationships was examined by 1) fitting the linear dose-response model using each of the 100 realizations of dose separately, and 2) using a Bayesian approach to calculate deattenuated estimates of the regression slope parameter in the sex-stratified logistic model.

It was not assumed that the out-of-area participants were unexposed to ^{131}I from Hanford. Indeed, results of the HTDS Pilot Study suggested that many out-of-area participants lived in locations near the HEDR domain at various times during 1945-1957. Alternative methods of assigning a dose estimate for out-of-area participants were developed, and these dose estimates were used to assess the sensitivity of dose-response results to assumptions about the doses for out-of-area participants.

The distribution of doses was quite skewed, with large numbers of comparatively low doses and small numbers of quite high doses. Therefore analyses were performed to assess whether the dose-response results might be inordinately influenced by the high dose participants. In particular, two empirical checks were made to assess whether the estimated regression coefficient adequately represents the dose-response relationship over the lower dose range.

Information released by the U.S. National Cancer Institute (NCI) shortly before and during October 1997, indicated that people living in the contiguous 48 states during the 1950s and 1960s were exposed to various levels of ^{131}I released from the Nevada Test Site (NTS). The material released by NCI included estimates of dose for representative individuals in all counties in the 48 states, as well as more detailed data regarding estimated dose by individual test detonation, county, and age. Limited preliminary comparisons for HTDS participants suggested that in many cases the reported NTS dose estimates were comparable to or even greater than the estimated Hanford doses. Therefore it was judged necessary to evaluate exposure to ^{131}I from the NTS as a potential confounding factor. For each participant in the HTDS, the "estimated NTS dose" was defined specifically as the thyroid dose from ^{131}I entering the atmosphere from tests conducted at NTS between 1951 and 1957, inclusive, as estimated from data made publicly available by NCI. A categorical variable representing each living evaluable participant's relative level of exposure to ^{131}I from the NTS was calculated for use in the analyses of potential confounding.

V. Summary of Dose-Response Results

The primary evaluation of dose-response relationships focused on twelve categories of thyroid disease, hyperparathyroidism, and ultrasound-detected abnormalities of the thyroid. For each of these 14 outcome categories a primary case definition was specified based on the most definitive diagnostic criteria available. Diagnostic information obtained from the HTDS evaluation and diagnostic information which was well documented in medical records and met criteria for HTDS diagnoses was considered to be the most definitive and of the highest quality. The primary analysis for each outcome was therefore restricted to cases defined according to these two sources. The principal dose-response analysis used this primary definition of outcome, individual radiation dose estimates (the median of CIDER's 100 realizations for each individual) based on individual residence history, dietary consumption data from the CATI when available, and HEDR default values when such data were not available. The results from these analyses using the primary outcome definition constitute the principal findings of the HTDS.

Additional criteria were also defined for each outcome category, to identify cases using less definitive diagnostic criteria, e.g., information obtained from prior medical records that did not meet HTDS criteria, or reports of a diagnosis by a participant or CATI respondent which could not be confirmed by the HTDS evaluation or medical records. Although the principal findings of the HTDS are based on the primary outcome definition, dose-response analyses were also conducted for each of these alternative definitions with less definitive diagnostic criteria. In addition, dose-response analyses were conducted for six outcome categories based on the results of laboratory assays, and for thyroid mass estimated from the ultrasound scan. Dose-response analyses for all disease and thyroid UDA outcomes were repeated using two alternative sets of individual dose estimates, and two alternative representations of exposure that did not use the CIDER program to estimate individual radiation doses. Efforts were also made to evaluate the influence of uncertainties in individual dose estimates on the fitted dose-response relationships for the primary case definition in each outcome category.

In overall summary of the dose-response results, there was no evidence of a statistically significant association between estimated thyroid radiation dose from Hanford and the cumulative incidence of any of the 14 primary outcomes. There was also no evidence of any statistically significant dose-response relationship for any of the alternative definitions of outcome. The findings were essentially unchanged for analyses based on either of the two alternative sets of individual dose estimates. The results remained the same after taking into account several factors that might confound the relationship between radiation dose and the outcome of interest. There was no evidence of any statistically significant dose-response for any outcome that might be different from the linear model used in the primary analyses (e.g., a linear-quadratic or logistic relationship). Incorporation of uncertainty in the dose estimates did not significantly change the primary results for any of the outcomes or change the overall conclusions of the study. Summarized below are the main findings for each of the primary outcomes investigated.

Thyroid Cancer

Twenty (0.6%) of the 3440 living evaluable participants were diagnosed with thyroid cancer; 13 women (0.7%) and 7 men (0.4%). In all but one case, the diagnosis was based on histologic evidence from the HTDS examination (12) or prior histologic evidence (7). Using the primary definition (19 total cases; 14 in-area) and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of thyroid cancer did not increase significantly with estimated dose ($p = 0.25$), with an estimated slope of 0.002 per Gy, and Bonferroni-adjusted 95% confidence interval (CI) ranging from less than –0.001 to 0.017 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Incorporation of uncertainty in the dose estimates did not significantly change the primary results.

Benign Thyroid Nodule

Two hundred and forty-nine (7.2%) of the 3440 living evaluable participants had a diagnosis of benign thyroid nodule based on histologic or cytologic evidence arising from the HTDS examination or

from a prior diagnosis which met HTDS diagnostic criteria; 170 (9.7%) women and 79 (4.7%) men. An additional 38 participants (1.1%) had HTDS or prior diagnoses classified as clinical (i.e., palpable nodule with no cytology or histology available), and another 10 (0.3%) had diagnoses based solely on a report by the participant or his/her CATI respondent. Using the primary definition (249 total cases; 235 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of benign thyroid nodule did not increase significantly with estimated dose ($p = 0.68$), with an estimated slope of –0.008 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.022 to 0.041 per Gy. Analyses that considered less definitive criteria to identify cases, as well as other disease outcomes related to benign nodules (e.g., benign nodules and nodules suspicious for follicular neoplasm, benign nodule excluding non-neoplastic disease, solitary nodule detected without ultrasound, benign nodule excluding colloid-only nodules, and benign colloid nodules), and analyses which considered alternative dose estimates or representations of exposure, revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Total Thyroid Neoplasia

This outcome was defined to include participants with thyroid cancer based on HTDS or prior histology, or benign thyroid nodule with a histologic type of follicular adenoma, based on HTDS or prior histology. A total of 33 (1.0%) of the 3440 living evaluable participants were included in this category; 20 (1.1%) women and 13 (0.8%) men. Using the primary definition (33 total cases; 28 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of total thyroid neoplasia did not increase significantly with estimated dose ($p = 0.42$), with an estimated slope of 0.001 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.003 to 0.022 per Gy. Analyses using alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Incorporation of uncertainty in the dose estimates did not significantly change the primary results.

Any Thyroid Nodule

This outcome was defined by the diagnosis of one or more of the following: benign thyroid nodule, thyroid cancer, or nodule suspicious for follicular neoplasm. A total of 281 (8.2%) of the 3440 living evaluable participants had this outcome based on histologic or cytologic evidence arising from the HTDS examination or from a prior diagnosis; 193 (11.0%) women and 88 (5.2%) men. Another 39 (1.1%) were based on HTDS or prior clinical diagnoses (i.e., palpable nodule with no available cytology or histology), and 10 living evaluable participants had diagnoses of any thyroid nodule based solely on reports from the participant or his/her CATI respondent.

Using the primary definition (281 total cases; 261 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of any thyroid nodule did not increase significantly with estimated dose ($p = 0.65$), with an estimated slope of –0.007 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.023 to 0.043 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Hypothyroidism

Two hundred and sixty-seven (7.8%) of the 3440 living evaluable participants had a diagnosis of hypothyroidism based on the HTDS evaluation or on medical records with supporting documentation; 204 (11.7%) women and 63 (3.7%) men. An additional 105 (3.1%) living evaluable participants had a diagnosis of hypothyroidism based on medical records but without supporting documentation, and 30 (0.9%) were inferred from past or current thyroxine therapy. This latter group consisted of participants who were taking thyroid hormone replacement, but in whom no medical records were available to confirm the

original diagnosis of hypothyroidism. There were also 193 (5.6%) cases based solely on reports of hypothyroidism from the participant or his/her CATI respondent.

Using the primary definition (267 total cases; 246 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of hypothyroidism did not increase significantly with estimated dose ($p = 0.61$), with an estimated slope of –0.006 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.016 to 0.047 per Gy. Analyses which considered less definitive criteria to identify cases, as well as permanent hypothyroidism, and analyses which considered alternative dose estimates or representations of exposure, revealed no statistically significant dose-response relationships, although the estimated regression coefficients from logistic regression analyses using less definitive criteria to identify cases were somewhat larger. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Autoimmune (Hashimoto's) Thyroiditis

A total of 625 (18.2%) of the 3440 living evaluable participants had a diagnosis of autoimmune thyroiditis based on the HTDS evaluation or medical records with supporting documentation; 403 (23.1%) women and 222 (13.1%) men. Another three cases were based on medical records without supporting documentation, and one case was based solely on a report by the participant or his/her CATI respondent.

Using the primary definition (625 total cases; 582 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of autoimmune thyroiditis did not increase significantly with estimated dose ($p = 0.82$), with an estimated slope of –0.026 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.057 to 0.044 per Gy. Analyses which considered less definitive criteria to identify cases, additional outcomes related to the assay for antithyroid immune response, and autoimmune thyroiditis in combination with non-iatrogenic, permanent hypothyroidism, as well as analyses which considered alternative dose estimates or representations of exposure, revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Graves Disease

A total of thirty-four (1.0%) of the 3440 living evaluable participants had a diagnosis of Graves Disease based on the HTDS evaluation or on medical records with supporting documentation; 28 (1.6%) women and 6 (0.4%) men. Three (0.1%) living evaluable participants had a diagnosis of Graves Disease based on medical records without supporting documentation, and an additional thirteen (0.4%) were based solely on a report from the participant or his/her CATI respondent.

Using the primary definition (34 total cases; 32 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of Graves Disease did not increase significantly with estimated dose ($p = 0.56$), with an estimated slope of –0.001 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.002 to 0.024 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Autoimmune Thyroid Disease

Autoimmune thyroid disease was defined by a diagnosis of autoimmune (Hashimoto’s) thyroiditis or Graves disease based on the HTDS evaluation or medical records with supporting documentation. A total of 659 (19.2%) of the 3440 living evaluable participants were included in this category; 431 (24.7%) women and 228 (13.5%) men. These included 625 with autoimmune (Hashimoto’s) thyroiditis and 34

others with diagnoses of Graves disease. An additional 4 (0.1%) living evaluable participants had a diagnosis of autoimmune thyroid disease based on medical records without supporting documentation (three with autoimmune thyroiditis, one with Graves disease). Eleven others (0.3%) were based solely on a report by the participant or his/her CATI respondent (one with autoimmune thyroiditis, 10 with Graves disease).

Using the primary definition (659 total cases; 614 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of autoimmune thyroid disease did not increase significantly with estimated dose ($p = 0.80$), with an estimated slope of –0.024, and Bonferroni-adjusted 95% CI ranging from less than –0.058 to 0.048 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Hyperthyroidism

A total of 161 (4.7%) of the 3440 living evaluable participants were diagnosed with hyperthyroidism based on the HTDS evaluation or medical records with supporting documentation; 134 (7.7%) women and 27 (1.6%) men. An additional 14 (0.4%) living evaluable participants had a diagnosis of hyperthyroidism based on medical records without supporting documentation, and 21 (0.6%) were based solely on a report from the participant or his/her CATI respondent. It is important to note that these 196 cases included a substantial number of iatrogenic cases caused by excess thyroid hormone replacement. Since endogenous hyperthyroidism (hyperthyroidism not caused by thyroid hormone over-replacement) was of particular importance, analyses that focused on cases of non-iatrogenic hyperthyroidism were emphasized in this study.

Using the primary definition (161 total cases; 155 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of hyperthyroidism did not increase significantly with estimated dose ($p = 0.22$), with an estimated slope of 0.011 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.008 to 0.052 per Gy. Analyses that considered less definitive criteria to identify cases, as well as non-iatrogenic hyperthyroidism, and analyses which considered alternative dose estimates or representations of exposure, revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Multinodular Thyroid Gland

A total of 95 (2.8%) of the 3440 living evaluable participants had a diagnosis of multinodular thyroid gland based on the HTDS evaluation; 73 (4.2 %) women and 22 (1.3 %) men. An additional nineteen (0.6%) living evaluable participants had a diagnosis of multinodular thyroid gland based on medical records, and one diagnosis was based solely on a report from the participant or his/her CATI respondent.

Using the primary definition (95 total cases; 85 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of multinodular thyroid gland did not increase significantly with estimated dose ($p = 0.88$), with an estimated slope of –0.006 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.014 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Simple Goiter

The diagnosis of simple goiter was uncommon, with only 14 (0.4%) of the 3440 living evaluable participants having this diagnosis based on HTDS evaluation; 9 (0.5%) women and 5 (0.3%) men. Another 28 (0.8%) had diagnoses based on medical records, and for an additional 28 (0.8%) the diagnosis was based solely on a report by the participant or his/her CATI respondent.

Using the primary definition (14 total cases; all in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the cumulative incidence of simple goiter did not increase significantly with estimated dose ($p = 0.74$), with an estimated slope of –0.001 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.012 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Incorporation of uncertainty in the dose estimates did not significantly change the primary results.

Other Thyroid Disease

Four living evaluable participants, all in the in-area group, had diagnoses of other thyroid disease based on their HTDS examinations or medical records with supporting documentation. These included two cases of subacute thyroiditis, one case of familial thyroglobulin binding deficiency, and one case of secondary hypothyroidism. The first alternative definition added only two cases of subacute thyroiditis with diagnoses based on medical records without supporting documentation. For both the primary and first alternative definition of other thyroid disease, there were too few cases for meaningful estimation of the radiation dose-response.

The second alternative definition added 20 participants, primarily with participant or CATI respondent reports of past thyroid disease of unknown type. This brought the total number of cases to 26, of whom four were out-of-area participants. Based on maximum likelihood analysis of the sex-stratified linear probability model using this case definition, the estimated slope was slightly greater than zero (0.002 per Gy), with Bonferroni-adjusted 95% confidence interval ranging from less than –0.002 to 0.024 per Gy, providing no evidence that the cumulative incidence increased significantly with increasing dose (one-tailed $p = 0.39$). Because the number of cases in this category was small, and the diagnoses were heterogeneous and mostly unknown, further analyses of this outcome were not performed.

Hyperparathyroidism

A total of 12 (0.3%) living evaluable participants had a diagnosis of hyperparathyroidism based on the HTDS evaluation or on medical records with supporting documentation; 10 (0.6 %) women and 2 (0.1%) men. Another two diagnoses were based on a report from the participant or his/her CATI respondent. One additional living evaluable participant who did not meet the study's criteria for hyperparathyroidism nevertheless had an elevated calcium level in the presence of a high normal PTH level, when the PTH should have been suppressed, highly suggestive of hyperparathyroidism. This participant was included as a case in an additional analysis.

Using the primary definition (12 total cases; 11 in-area), the cumulative incidence of hyperparathyroidism did not increase significantly with estimated dose ($p = 0.61$), with an estimated slope of –0.0001 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.013 per Gy. Analyses that considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Incorporation of uncertainty in the dose estimates did not significantly change the primary results.

Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

The thyroid gland was visible in the ultrasound examinations of 3429 of the 3440 living evaluable participants. For 11 participants the thyroid was not visible, 10 because of thyroid surgery and one because the sonographer couldn't adequately visualize the thyroid. Among the 3429 whose thyroids were visible, 1596 (46.5%) had one or more thyroid UDAs; 964 (55.5 %) women and 632 (37.4 %) men. Ultrasound findings were categorized as palpable thyroid UDAs (224 or 6.5%), nonpalpable focal thyroid UDAs (1309 or 38.2%), and diffuse thyroid UDAs (458 or 13.4%). All three types of UDA were more frequent among women than men. Ultrasound-detected thyroid abnormalities were based only on the HTDS evaluation, not on any prior ultrasound scans.

Based on maximum likelihood analysis of the sex-stratified linear probability model, the prevalence of any UDA (1596 total cases; 1481 in-area) did not increase significantly with estimated dose ($p = 0.21$), with an estimated slope of 0.031 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.059 to 0.116 per Gy. Similarly, the prevalence of palpable UDA (224 total cases; 204 in-area) did not increase significantly with estimated dose ($p = 0.95$), with an estimated slope of –0.018 per Gy. The Bonferroni-adjusted lower 95% confidence limit was not estimated due to the magnitude of the negative slope estimate, however the upper confidence limit was 0.015 per Gy. The prevalence of nonpalpable focal UDA (1309 total cases; 1217 in-area) also did not increase significantly with estimated dose ($p = 0.23$), with an estimated slope of 0.027 per Gy and Bonferroni-adjusted 95% CI ranging from –0.061 to 0.115 per Gy. Analyses of all three types of ultrasound abnormalities in relation to alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Additional analyses were performed to assess whether ultrasound abnormalities might be precursors to radiation-induced clinical disease. These analyses evaluated whether increasing dose was associated with increasing prevalence of large thyroid UDAs, increasing number of thyroid UDAs, or the presence of diffuse thyroid UDAs. To assess whether the dose-response results might be affected by the size of focal thyroid UDAs, three additional outcomes were analyzed. These included the presence of a focal UDA with maximum dimension at least 5 mm, the presence of a focal UDA with maximum dimension at least 10 mm, and the presence of a focal UDA with average dimension at least 15 mm. These additional analyses applied only to palpable and nonpalpable focal thyroid UDAs, since diffuse UDAs were not defined by any size criterion. In none of these additional analyses was there any evidence that the risk of having a focal UDA of a particular size increased with increasing dose ($p=0.64$, 0.88 and 0.53 for the presence of focal UDA with maximum dimension of 5 mm, maximum dimension of 10 mm and average dimension of 15 mm, respectively).

To assess whether the number of thyroid UDAs detected in individual participants might increase in relation to estimated thyroid radiation dose, the numbers of focal thyroid UDAs with maximum dimension ≥ 5 mm, maximum dimension ≥ 10 mm, and average dimension ≥ 15 mm were counted for each living evaluable participant with an HTDS ultrasound examination. No statistically significant dose-response was found between estimated thyroid radiation dose and the average number of focal thyroid UDAs ($p = 0.80$, 0.48 and 0.43 for the number of thyroid UDAs meeting the three size criteria, respectively).

The prevalence of diffuse thyroid UDA (458 total cases; 428 in-area) did not increase significantly with estimated dose ($p = 0.14$), with an estimated slope of 0.029 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.029 to 0.100 per Gy. Analyses that considered alternative dose estimates or representations of exposure revealed no statistically significant dose-response relationships. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not significantly change the primary results.

Laboratory Tests and Thyroid Mass

Of the 3191 living evaluable in-area participants, 3183 (99.7%) provided a blood specimen at the HTDS clinic. Several laboratory assays were conducted to evaluate thyroid function, anti-thyroid antibody response, and serum calcium level. In addition to the dose-response analyses conducted of specific thyroid disease outcomes, which incorporated information from these tests in the determination of the diagnosis, dose-response analyses were also conducted to investigate whether there were associations between the laboratory values from these tests and estimated thyroid radiation dose from Hanford (i.e., regardless of thyroid disease diagnosis).

Thyroid stimulating hormone (TSH) levels were measured for all participants who provided a blood specimen. Of the 3183 living evaluable in-area participants who provided blood samples, 222 were receiving exogenous thyroid hormone at the time of their HTDS clinic and were excluded from the analyses of TSH. Among the remaining 2961 living evaluable in-area participants, three different TSH assays were used during the study. There was no statistically significant trend of average TSH level in relation to estimated radiation dose for any of the three assays considered either separately or in a combined analysis. Free thyroxine index (FTI) was analyzed, also excluding the 222 participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic. There was no significant trend of FTI in relation to estimated radiation dose (two tailed $p = 0.23$). Three different tests for antithyroid antibody response (anti-TPO, AMA, and anti-TG) were used over the course of the study. There was no significant trend of any assay result in relation to estimated radiation dose ($p = 0.66$ for anti-TPO, 0.52 for AMA, and 0.20 for anti-TG).

Serum calcium levels were measured in an effort to identify participants with hypercalcemia that might be secondary to hyperparathyroidism. Of the 3183 living evaluable in-area participants who provided blood samples, 227 with diagnoses of hypothyroidism or hyperthyroidism based on the HTDS examination were excluded from the primary analysis of serum calcium levels. Two additional participants did not have serum calcium data due to insufficient volumes of collected blood. There was a statistically significant trend of decreasing serum calcium level in relation to increasing radiation dose ($p = 0.0074$), with an estimated slope of –0.09 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.16 to –0.01 per Gy. Although there is no readily apparent explanation for this result, this finding deserves further comment. First, the outcome for which calcium was being measured, hyperparathyroidism, was not found to be associated with radiation dose. Second, the dose effect occurred within the normal range of calcium values. For both women and men, the estimated background means were about $9.2 \pm .01$, consistent with the normal range of the test (8.4 to 10.2). Only 0.9% of the cohort had low calcium levels less than 8.4 (hypocalcemia). There was no statistically significant relationship between hypocalcemia and radiation dose. Third, even at a dose of 3000 mGy to the thyroid, which is larger than the maximum estimated dose for any study participant, the mean serum calcium levels predicted by the regression model were well within the normal range. Therefore, despite the *statistically* significant decrease in calcium levels with increasing dose, the resulting effect or clinical impact does not appear to be *clinically* significant.

Estimates of thyroid mass were available for 3400 living evaluable participants for whom both lobes of the thyroid were visible on ultrasound; 3153 were in-area participants. There was no statistically significant trend of thyroid mass in relation to estimated radiation dose ($p = 0.98$).

VI. Summary Comments and Conclusions

The HTDS was conducted to determine whether exposure to atmospheric releases of radioactive iodine, in particular ^{131}I, from the Hanford Nuclear Site between 1944 and 1957 resulted in increased thyroid disease among those exposed. The study evaluated twelve categories of thyroid disease, hyperparathyroidism, ultrasound-detected abnormalities of the thyroid, the results of several laboratory tests for thyroid function, anti-thyroid antibody and serum calcium level, and thyroid mass. The primary analysis (based on HTDS diagnostic criteria of the highest level of certainty) utilized an estimate of thyroid radiation dose for each individual based on information about their residence history and dietary consumption patterns during the times of the Hanford releases. Additional analyses were conducted using several alternative methods for estimating dose, both quantitative and qualitative, including methods that were independent of the HEDR models. The primary analyses were based on a linear dose-response model, adjusting for the effects of differences in response by sex, although alternative models for the shape of the dose-response were also investigated. The potential confounding or dose-response modifying effects of a number of lifestyle factors and indicators of other radiation exposure were evaluated. All primary dose-response analyses were repeated to include adjustments for uncertainty in the individual radiation dose estimates.

This study found no statistically significant association between dose to the thyroid from Hanford radiation and 1) cumulative incidence of any of the disease outcomes; 2) prevalence of ultrasound-detected thyroid abnormalities; or 3) thyroid laboratory tests or thyroid mass. There was also no statistically significant dose-response for hyperparathyroidism, although increasing thyroid dose was significantly associated with a decrease in average serum calcium level. Although the explanation for this result is not clearly apparent, the finding does not appear to be of clinical significance. These results remained the same when alternative methods of assessing radiation dose were used, and after accounting for uncertainty in dose estimation. Based on data available regarding the tracing and enrollment of study participants, there is no evidence that the absence of a dose-response relationship is due to bias in selection of the cohort, loss to follow-up, or enrollment and participation.

Although no statistically significant dose-response was found for any of the disease outcomes in this study, many study participants had thyroid disease. A considerable effort was made to assess the world literature on the prevalence of the major thyroid and parathyroid disease outcomes evaluated in the HTDS. Studies selected for review were those conducted in other locations and most comparable to the HTDS for the outcomes of thyroid nodules, thyroid cancer, hypothyroidism, autoimmune thyroiditis, hyperparathyroidism, and thyroid UDAs. This was done in order to compare the disease experience of the HTDS cohort to what might reasonably be expected based on the experience in other populations not exposed to Hanford radiation. As discussed in the Section X.E of the Report, comparisons of this type are imperfect and must be interpreted with great caution. Differences in prevalence estimates between the HTDS cohort and other populations may well reflect differences in any of a number of factors other than exposure to radiation from Hanford. Nevertheless, from review of these studies, it appears that estimates of cumulative incidence derived from the HTDS are well within the range and are consistent with published estimates. There is no indication that the levels of thyroid or parathyroid disease occurrence in the HTDS cohort are systematically different, or higher, than what has been reported around the world in a variety of different circumstances.

Given the differences between the radiation exposure circumstances at Hanford and those of other populations in which radiation-related risks of thyroid disease have been studied, the findings of this study are not inconsistent with the current published literature regarding the effect of exposure to ^{131}I and the risk of thyroid and parathyroid disease. This is particularly so given the relatively small magnitude of the estimated thyroid radiation doses in HTDS study participants (mean = 174 mGy) and the relatively protracted nature of the exposure over time. There is little evidence in the literature to suggest that people exposed to ^{131}I at the levels found in this study over a period of months or years would experience higher rates of thyroid or parathyroid disease as a result of their exposure.

Nevertheless, a lingering question for many may be whether the uncertain nature of the dose estimation used in the primary analyses is so great that it renders the quantitative dose-response results

inconclusive. The study has attempted to address this possibility in three ways. First, alternative qualitative methods of assigning exposure were used. Results from these analyses were consistent with those from the quantitative dose-response analyses. Second, two different approaches were employed to evaluate the impact of dose uncertainty on the primary risk estimates. Neither resulted in findings that were significantly different from those ignoring such uncertainty. Third, the impact of dose uncertainty on study power was assessed using simulation methods. These analyses revealed that the reduction in statistical power due to uncertainty in dose estimation was modest, and that even after accounting for such uncertainty the study had adequate statistical power to detect effects as small or smaller than those in the existing published literature. Although any epidemiologic study is limited to some extent by uncertainty in the assessment of exposure, the impact of such uncertainty on the power of the study and the estimation of risk is seldom addressed to the extent attempted here. Further, the fact that epidemiologic investigations are inherently "uncertain" does not imply complete randomness or unpredictability, nor does it mean that reasonable conclusions cannot be drawn from such studies.

In conclusion, the results of the HTDS provide no evidence of a statistically significant association between increasing thyroid radiation dose from Hanford and the cumulative incidence of any of the primary outcomes studied. These findings do not definitively rule out the possibility that Hanford radiation exposures are associated with an increase in one or more of the outcomes under investigation. However, it does mean that if such associations exist, they were likely too small to detect using the best epidemiologic methods available.

I. INTRODUCTION

The Hanford Thyroid Disease Study (HTDS) was conducted by a team of investigators at the Fred Hutchinson Cancer Research Center (FHCRC) under contract to the Centers for Disease Control and Prevention (CDC) Radiation Studies Branch. The Study Management Team (SMT) which had primary responsibility for the design and conduct of the investigation, consisted of Scott Davis, Ph.D. (epidemiology), Kenneth Kopecky, Ph.D. (biostatistics), and Thomas Hamilton, M.D., Ph.D. (endocrinology). Bruce Amundson, M.D. (family medicine) was a member of the SMT through August 1998. Ms. Peggy Adams Myers served as Project Manager through the release of the Draft Final Report. Ms. Beth King assumed responsibility for project management thereafter. In addition to the FHCRC team, the study employed Dr. Robert Griep as an expert consultant on thyroid disease. Dr. Bruce Kulander served as the pathologist who reviewed all pathological specimens. Four radiologists at Seattle Nuclear Medicine/Ultrasound Associates interpreted the thyroid ultrasound scans. Administrative, statistical, and technical staff reported directly to the Project Manager and the SMT. The clinical component of the HTDS was directed by Dr. Hamilton, with the assistance of the HTDS study physicians in conducting thyroid examinations. Study operations were based at the FHCRC in Seattle, with a field office in the Tri-Cities for the Subject Tracing component.

The CDC was kept informed on a monthly basis of progress in the design and conduct of the study, and provided technical support as needed by the FHCRC. Mr. Michael Sage and Mr. Michael Donnelly served as the Project Officers. Dr. Paul Garbe was the primary scientific liaison. In addition, an Advisory Committee was appointed for this study by the Secretary of the Department of Health and Human Services to provide advice and consultation to the CDC and the SMT.

The technical approach to this research project was divided into three phases. The first phase involved the development of the study protocol and preparation for the Pilot Study. These preparations included the appointment and convening of the Advisory Committee and approval of the protocol by the federal Office of Management and Budget (OMB) and the Institutional Review Board (IRB) of the FHCRC. This phase began upon award of the contract in September 1989, and was concluded in late 1992. The other two phases of the study, the Pilot Study and the Full Study, are discussed further below.

The study was conducted as a follow-up prevalence study. That is, potential participants were selected on the basis of presumed past level of exposure to radioactive iodine from Hanford, based on place and year of birth. Participants were located and evaluated for the presence or history of thyroid disease. Information was also collected regarding each participant's residence and dietary history in order to estimate his or her thyroid radiation dose from Hanford. The primary analyses focused on living participants who received medical examinations to detect thyroid disease, and for whom individual thyroid radiation doses could be estimated using the dosimetry system developed by the Hanford Environmental Dose Reconstruction (HEDR) Project and the information collected by the HTDS. Although the effects of primary interest are defined by three categories of thyroid disease (hypothyroidism, benign thyroid nodules, and thyroid cancer), information regarding all forms of thyroid disease were recorded as part of the study and are included in the overall analysis. In addition, hyperparathyroidism was evaluated by screening individuals for hypercalcemia. Since the aim of the study was to investigate whether risks of the thyroid diseases were increased by exposure to Hanford's ^{131}I, the analysis examined whether the cumulative incidence of these diseases increased with increasing dose to the thyroid.

The methods of the study can be summarized as follows. Potential study participants were selected from birth records to form a cohort for follow-up. People likely to have lived in a seven-county geographic area surrounding the Hanford Site were selected to ensure as much as possible that the cohort contained people with a wide range of radiation doses to the thyroid (e.g., from the highest doses to very low doses). Attempts were made to trace and locate each individual in the cohort. Once located, each person was invited to a medical clinic for a thorough diagnostic evaluation for thyroid disease. At the clinic, each study participant: 1) underwent a personal interview regarding details of his/her residential,

medical, and personal histories; 2) provided a blood sample for thyroid function tests, antibody markers for autoimmune thyroiditis, and serum calcium determination; 3) received a thyroid ultrasound examination; and 4) received a physical examination of the thyroid by two physicians independently of one another. For those found to have palpable thyroid nodules or nonpalpable ultrasound detected thyroid nodules ≥ 1.5 cm (average of three dimensions), permission was sought to conduct a fine needle aspiration to provide more complete diagnostic information. To verify reports of thyroid diseases that occurred in the past, medical records and pathology specimens were sought and reviewed in a uniform manner.

Prior to the participant's clinic visit, an attempt was made to interview the mother, or other close relative knowledgeable about aspects of the participant's childhood that influenced the radiation dose he or she received from Hanford. The information collected in this interview was used to estimate radiation dose to the thyroid using algorithms developed by Battelle Pacific Northwest Laboratory as part of the Hanford Environmental Dose Reconstruction (HEDR) Project. Detailed descriptions of each component of the study fieldwork are found in section V of this report.

Following the development and approval of the study protocol, the research was conducted in two subsequent phases. The first was a Pilot Study. The primary purpose of this phase was to evaluate the feasibility of the methods proposed and to develop the specific operational procedures and data collection instruments needed for a Full Study. Once the results of the Pilot Study indicated that it was feasible to conduct a successful full-scale epidemiologic study, the second stage was implemented to complete the remaining fieldwork for the Full Study. This approach allowed the accumulation of information and experience prior to initiation of the more costly full-scale study. This also allowed for the possibility that the design and procedures for the Full Study could be modified if necessary to account for the realities of the field environment.

Eleven Pilot Study objectives were specified in the original HTDS protocol (1). These objectives dealt with both logistical and statistical issues. Logistical issues to be evaluated included: 1) the efficacy and success rates of the fieldwork procedures, including the use of birth certificates to identify potential study participants; 2) the ability to trace and locate persons identified; 3) the ability to collect information for use in estimating thyroid radiation dose; 4) the success in bringing participants to clinics for thyroid examinations and 5) the costs of these activities. Statistical issues to be evaluated included: 1) estimating the distributions of radiation dose to the thyroid among groups of individuals defined by place of birth; 2) evaluating the suitability of the areas from which participants were selected to ensure a cohort of individuals with a full range of doses; and 3) calculation of the statistical power that could be reasonably achieved in a Full Study and the sample size required to do so. A detailed report of the results of the Pilot Study was submitted to the CDC on January 24, 1995. A summary of the findings of that report is included here as Appendix 1 (Executive Summary of the Pilot Study Report).

It should be emphasized that in testing the feasibility of the study design, it was important to evaluate procedures and instruments for participants who were likely to have received high doses from Hanford radiation releases, as well as for those who were not likely to have received such doses. There was concern that the degree to which individuals could be identified, traced, located, and recruited into the study might be influenced to a large extent by their physical proximity to the Hanford Site and their perception of any direct threat to their own health from Hanford. Thus, a very important aspect of the Pilot Study was to evaluate the success of including people who lived in varying proximity to the Hanford Site.

It is also important to emphasize that the Pilot Study was not designed to assess health outcomes in relation to radiation dose. Instead, the Pilot Study was designed to: 1) test the feasibility of the proposed field logistics; 2) estimate the radiation doses likely to have been received among study participants and, therefore, to determine the distribution of doses according to factors such as geographical area (e.g., urban vs. rural), age, and sex; and 3) derive the information necessary to adequately plan a Full Study that would be capable of determining whether radiation releases from Hanford resulted in an increased risk of thyroid disease or hyperparathyroidism. The number of participants included in the Pilot Study was too small and the individual radiation dose estimates available from the HEDR Project were too preliminary to enable

any formal evaluation of adverse health effects in the pilot phase of the HTDS. Thus, no estimates of thyroid disease or hyperparathyroidism risk associated with exposure to radioactive iodine were reported at the conclusion of the Pilot Study. However, all data obtained from individuals who participated in the Pilot Study were included in the Full Study.

The Pilot Study was completed in late 1994. To maintain study operations in anticipation of conducting the Full Study, it was necessary to define a "transition phase" between the Pilot Study and Full Study. In the fall of 1993 the Federal Advisory Committee and the CDC gave approval to select an additional sample of 1000 potential participants to serve as a Transition Sample. Based on the information available at that time from the Pilot Study, it was decided that the Full Study would likely be implemented. Thus, the Transition Sample was selected to enable field operations to continue while the Pilot Study was completed and its results evaluated. This approach also shortened the time to complete the Full Study.

A report of the results of the Pilot Study was prepared and submitted to the CDC and the Advisory Committee in January 1995. Each of the objectives outlined for the Pilot Study in the study protocol was evaluated. The report's major conclusions were that:

1. The thyroid dose distributions obtained in the Pilot Study, which were the basis for the sample size and power calculations, were reasonably representative of what the overall dose distribution would be at the completion of the Full Study.

2. To achieve sufficient statistical power to detect an increase of 5% in thyroid neoplasia per Gray, it would be necessary to enroll a minimum of approximately 3200 living evaluable participants.

3. The basic design and data collection methods would remain the same.

4. Estimation of doses study participants would be conducted by HTDS staff by remote access to the HEDR computer programs at the CDC in Atlanta.

5. All births from the following years to mothers living in the indicated counties should be added to the cohort:
   a) 1942-1944: Remaining Richland, Pasco/Kennewick and Benton County
   b) 1940-1941: All of Benton and Franklin Counties
   c) 1940-1944: All of Adams County

The primary criterion for continuing with the Full Study was the ability to identify and recruit adequate numbers of people with a sufficient range of radiation doses. Specifically, the aim was to design the Full Study to have statistical power of at least 90% to detect a linear dose-response for the probability of having thyroid neoplasia (malignant or benign) with a slope of 0.0001 per rad (10% per Gy). If the results of the Pilot Study had indicated that it would not be possible to obtain at least 80% power to detect an effect of this magnitude, then consideration would have been given to terminating the study. However, the results of the Pilot Study (2) revealed that, not only did the procedures and plans work well for all aspects of the study, a conservative projection of statistical power of 80% to detect an increased risk of thyroid neoplasia of 5.0% per Gray was possible with some revisions to geographic areas and years of birth sampled. Section V.A. of this report discusses in detail the sampling utilized in the Full Study to achieve this level of power.

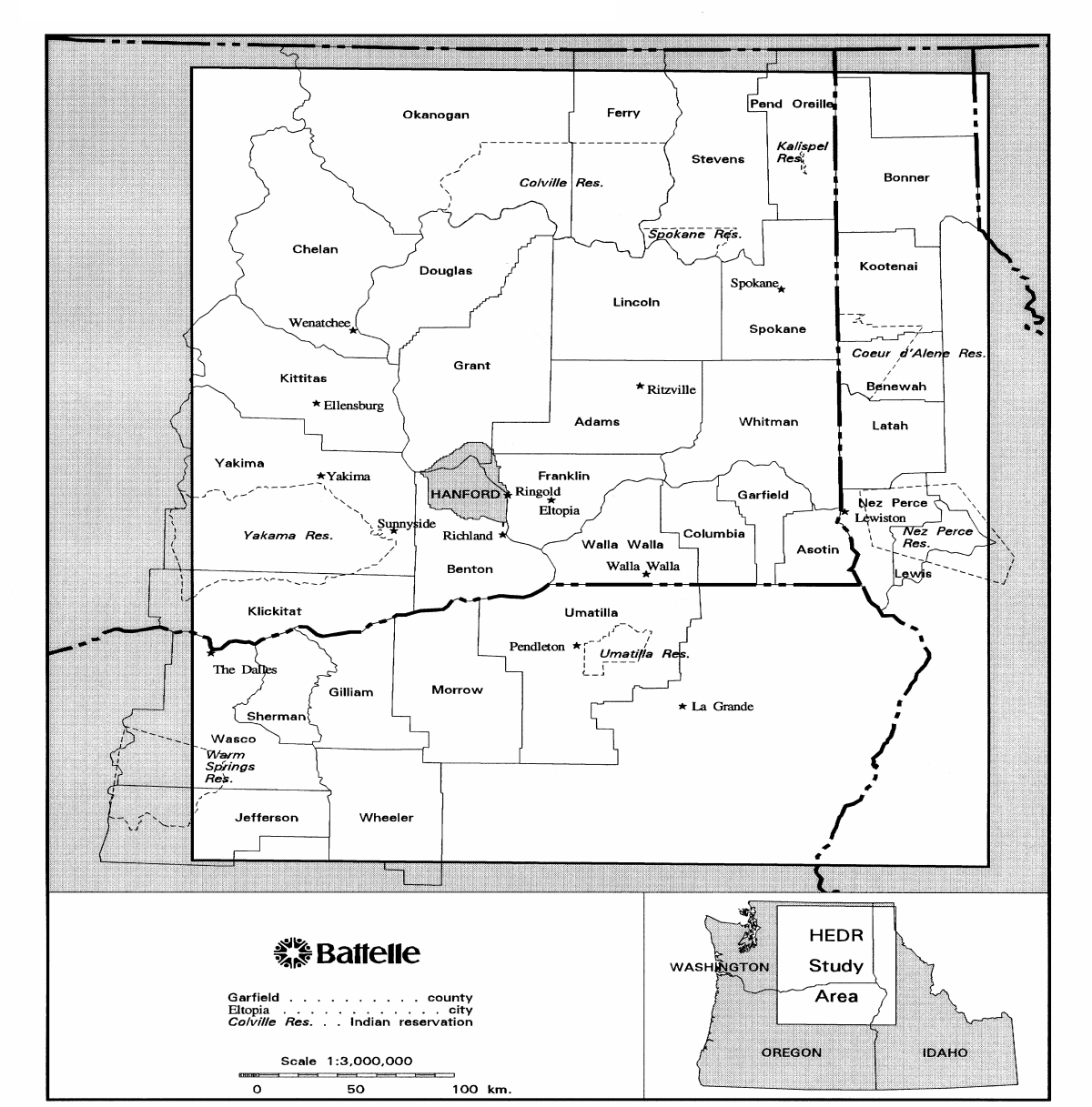
Thus, in February 1995, the Advisory Committee recommended to the CDC that the Full Study be done. The data collection phase of the Full Study was completed in late 1997, and was followed by a period of data analysis and the reporting of results. The purpose of this report is to document in detail the conduct of each phase of the HTDS, and the results of the analyses that were done.

II. BACKGROUND

A. Historical Perspective

The Hanford Nuclear Site occupies an area of approximately 560 square miles in southeastern Washington adjacent to the towns of Pasco, Kennewick, and Richland (Figure II.A-1). The facility was established in 1943 as part of the Manhattan Project to produce plutonium-239 for the development of the first nuclear weapons. The initial Hanford production reactor (B) became operational in September of 1944, and was followed by a second (D) in December. Two chemical separations plants, which constituted the second phase of plutonium production, began to operate in 1944 and 1945. By 1957 there were six additional production reactors and two fuel reprocessing plants on the Site.

Figure II.A-1 HEDR Study Area



* Used with permission

The creation of the Hanford Nuclear Site caused the regional population in the Columbia Basin to expand rapidly. Although the original construction force was large (approximately 50,000 persons), most had left the area by the end of 1945. However, major Hanford expansions in the late 1940s resulted in substantial population growth in the Tri-Cities area of Richland, Pasco, and Kennewick. Between 1945 and 1960, the population increased from approximately 40,000 to over 100,000 (3). In addition, Army anti-aircraft units numbering about 5000 troops per year served at Hanford beginning in 1950. Army personnel and construction workers and their families lived in a trailer-barracks enclave about five miles north of Richland. The counties surrounding the Hanford site, traditionally ranching and agricultural areas, continued to be populated by small, family farms. With the establishment of the Columbia Basin Irrigation Project and subsequent agricultural development, large numbers of new families moved into the region in the late 1950s.

In February 1986, largely as the result of repeated public requests from the Hanford Education Action League (Spokane, Washington) and the Environmental Policy Institute (Washington, D.C.), as well as requests from the Centers for Disease Control and Prevention and the State of Washington, the Department of Energy made available over 19,000 pages of documents (many of which were previously classified) describing radiation releases and environmental monitoring during the early years of plutonium production at Hanford. Based on information found in these documents and a subsequent Freedom of Information Act (FOIA) request, an additional 20,000 pages were made public in April 1987. Approximately 25,000 more pages have been released since late 1987.

Data contained in this material indicate that during the initial years of plutonium production at Hanford substantial quantities of radionuclides were released into the atmosphere, particularly during the first few years of production. In attempting to produce plutonium rapidly in 1944 and 1945, irradiated uranium was allowed to decay approximately 45 days before being treated for reprocessing. As a result, the subsequent chemical treatment of the irradiated uranium produced large atmospheric releases of gaseous radionuclides. A primary component of these releases was a radioactive isotope of iodine, iodine-131 (^{131}I).

Although it was uncertain exactly how much material was released from the Hanford site, it was apparent that hundreds of thousands of Curies (Ci) of ^{131}I were released into the atmosphere around Hanford between 1944 and 1956. Table II.A-1 displays two sets of estimates of annual emissions of ^{131}I from the fuels separation processing activities between 1944 and 1957. The largest releases occurred from 1944 through 1947, and in 1949 and 1951. Radiation monitoring data recently made available indicate that these atmospheric releases of ^{131}I were carried by prevailing winds and deposited in areas surrounding the Site. During the period of largest releases, Hanford scientists gradually discovered that ^{131}I deposited readily on sagebrush and sand (4-9). When the soil was disturbed by wind, construction, or agriculture, this material was subsequently re-circulated and re-deposited. Thus, attempts were made to establish tolerable limits for ^{131}I on vegetation (10-11) and to monitor ^{131}I levels in range animals (cattle and sheep) and jackrabbits (12-14). Results of such studies indicate that animals were heavily exposed in areas downwind of the Site (15), and that vegetation contamination levels on-site, particularly in the 200-area, were seldom below what were considered to be tolerable at that time (.20 μCi/kg) (16). In fact, an experiment conducted in December of 1949 deliberately released a cloud of ^{131}I into the atmosphere which drifted southeastward and northeastward from the Site causing vegetation readings as high as 107.3 μCi/kg in Kennewick (17). Releases from this so-called "Green Run" have been estimated to have been as high as 7780 Ci (18) or even 11,000 Ci (19).

Based on the data that initially became available, preliminary estimates were made of maximum doses to the thyroid that could have been received by persons living in close proximity to the Hanford Site during the years of atmospheric releases (20,21). Using environmental monitoring data for ^{131}I concentrations in vegetation, a variety of assumptions regarding agricultural production and dietary practices, and a U.S. Nuclear Regulatory Commission model to estimate thyroid doses, maximum doses were estimated (21) for residents of Richland and Pasco for four age groups: infants (0-1 yr), children (2-12 yr), teenagers (13-19 yr), and adults (20 and older). During the year of peak releases (1945), it is

estimated that the maximum annual thyroid dose to an infant may have been as high as approximately 2000 rad (20). Through 1947, maximum annual infant thyroid doses may have remained quite high (above 100 rad) with even higher periodic doses corresponding to larger atmospheric releases in the late 1940s and early 1950s. Similar estimates for infants have been proposed (20,22), with maximum annual thyroid doses decreasing to about one half these levels for children, about one quarter for teenagers, and about one-fifth for adults (17).

Table II.A-1. Estimates of Atmospheric Emissions of Radioactive Iodine from the Separations Plants Stacks

	^{131}I Ci (annual)	
Year	Anderson and Roberts Estimates*	Conklin Estimates**
1944	1700	54,000
1945	340,000	340,000
1946	76,000	76,000
1947	24,000	24,000
1948	1200	1200
1949	4670	7026 +
1950	2150	2734
1951	18,700	18,798
1952	967	996
1953	720	726
1954	540	544
1955	1200	1167
1956	370	NE++
1957	380	NE++
1944-1957	472,597	527,191

* Anderson JD. Emitted and Decayed Values of Radionuclides in Gaseous Wastes Discharged to the Atmosphere. ARH-3026, Atlantic Richfield Hanford Company, Richland Washington, 3/1/74.

* Roberts RE. History of Airborne Contamination and Control-200 Areas. HW-55569 RD, Hanford Atomic Products Operations, Richland Washington, 4/1/58, pg. 6 (16).

** Conklin AW. *Releases of Radioactivity from Hanford, 1944-1956. Memorandum dated July 1, 1987*. Department of Social and Health Services, Office of Radiation Protection, Olympia, Washington, 1989 (22).

+ Includes releases from the "Green Run". Recent estimates indicate these releases may have been higher than those shown: 7780 Ci (18) or 11 kCi (19).

++ NE – Not Estimated.

The disclosure of information in 1986 prompted widespread concern among people living near the Hanford Nuclear Site. Residents questioned whether such releases in the past may have increased their risk for developing disease, particularly cancer. Partially in response to their concerns, a panel of experts (the Hanford Health Effects Review Panel) was convened by the Centers for Disease Control in August 1986 to evaluate the data contained in the first 19,000 pages of documents. The Panel concluded that substantial quantities of radionuclides, particularly ^{131}I, had been released between 1944 and 1956 and that off-site radiation exposures, particularly to the thyroid, were probably high enough to warrant further study of health effects. Since ^{131}I concentrates in the thyroid, it was felt reasonable to expect that potential adverse health effects associated with the Hanford radiation releases would most likely be diseases of the thyroid. Thus, the Panel recommended: 1) a study of ^{131}I releases to estimate radiation doses that could have been received by area residents, and 2) a study of thyroid morbidity among persons known or suspected to have been exposed.

A second group was also formed during this time period (March 1986), the Hanford Historical Documents Review (HHDR) Committee, which consisted of representatives from the states of Oregon and

Washington as well as several Native American tribes. A Peer Review Panel of experts was appointed as an advisory group to the committee. The HHDR focused their activities on further review of the declassified documents, and worked to consider specific approaches to implementing the two principal recommendations of the Hanford Health Effects Review Panel.

As a result of these collective efforts, a comprehensive study of potential radiation doses began in 1987, initially funded by the United States Department of Energy. The objective of the Hanford Environmental Dose Reconstruction (HEDR) Project was to develop estimates of radiation doses that people may have received from Hanford operations. A primary focus of this effort was to estimate doses to the thyroid resulting from ^{131}I exposures. Preliminary evidence from the HEDR Project indicated that the contributions to thyroid dose from the shorter-lived isotopes of iodine (^{132}I, ^{133}I, ^{135}I) were probably negligible.

Directed by an independent Technical Steering Panel (TSP) of eighteen scientists and community representatives, Battelle Pacific Northwest Laboratories in Richland performed the technical work for HEDR. While originally performed under contract to the Department of Energy, in 1993 funding responsibility was transferred to the Centers for Disease Control and Prevention.

In July 1990, the TSP made public draft reports of Phase 1 of the HEDR Project. The objective of that phase was to establish, in terms of data availability and modeling capability, the feasibility of developing a system for estimating individual radiation doses and the uncertainties of those dose estimates. For radionuclides released to the atmosphere, this was accomplished by developing preliminary estimates of doses to the thyroid from ^{131}I (23). Although external exposure (immersion and groundshine), inhalation, and vegetable consumption pathways were considered, the primary emphasis was on the cow's milk pathway for ^{131}I, since this was anticipated to be the dominant source of exposure for many people. The Phase 1 region consisted of ten counties surrounding the Hanford Site. The population of that ten-county area was approximately 270,000 during the late 1940s. For this entire population, the median dose to the thyroid from ^{131}I ingestion of contaminated cow's milk during the period 1944-1947 was estimated to be 1.7 rad, and the 90th percentile was 15 rad. It was estimated that between 1.5% and 2% of the doses for this population exceeded 100 rad.

The preliminary results from HEDR Phase 1 also identified subpopulations that received generally higher exposures. In particular, infants and young children who drank milk from family cows that grazed on pasture in areas to the east, southeast, and south of Hanford may have received substantially higher exposures. Among such children, the median and 95th percentile doses were about 70 and 650 rad, respectively. Similar children living in this area who drank commercially produced milk had a distribution of doses nearly as high.

These preliminary estimates were refined in the later phases of the HEDR Project. The total amount of ^{131}I released into the air from Hanford between 1944 and 1972 was estimated in the HEDR model to be about 740,000 Ci (2.73×10^7 gigabecquerels), with 99.8% released through 1957 (24). The HEDR results, released in April 1994, contained thyroid radiation dose estimates for representative individuals who lived in areas surrounding the Hanford facility during the times of the radiation releases, and revealed that the deposition of radioactive ^{131}I was carried further from the Site than estimated in the Phase I results. Thus, relatively less radioactive ^{131}I was deposited in areas closest to the Site, while larger amounts were deposited further away than previously anticipated. This effectively decreased the highest dose estimates, while increasing the number of people with doses in the mid- and lower ranges. Thus, while the Phase II estimates indicated lower doses than those estimated in Phase I, the results continued to provide strong evidence that large numbers of people, particularly children, may have been exposed to thyroid doses in the range of 3 to 10 rad.

One of the major products of the HEDR Project was a collection of computer programs and databases that implemented the final HEDR models for calculating doses from radionuclides released into the environment from Hanford (25). One integrated set of these programs provided estimates of thyroid

radiation doses from Hanford's atmospheric releases of ^{131}I. This included models for the amounts of ^{131}I released into the atmosphere, for the transport of that ^{131}I through the air and its deposition onto vegetation and the ground, for its uptake into food and milk products and the distribution of those products, and for the calculation of thyroid dose from exposure to ^{131}I in environmental media (air, ground, and milk and other foods). In particular, a computer program called CIDER ("Calculation of Individual Doses from Environmental Radionuclides") combined data regarding estimated concentrations of ^{131}I in environmental media with information regarding characteristics of exposed individuals (e.g., location, diet, milk and food sources) to calculate individualized estimates of thyroid dose. The HEDR Project used the CIDER model to estimate thyroid doses for hypothetical representative individuals (26,27). As described elsewhere in this report, the HTDS also used the CIDER program to calculate dose estimates for the study participants.

The second principal recommendation of the Hanford Health Effects Review Panel, the initiation of a comprehensive thyroid morbidity study, was enabled by an act of Congress in 1988. Mandated by Senate Bill 2889, the CDC was directed to conduct a study of thyroid morbidity among persons who lived near the Hanford Nuclear Site between 1944 and 1957 (Appendix 2). Thyroid diseases were selected as the primary focus for a health outcome study based on the information described above regarding radiation releases, which suggested that ^{131}I was the radionuclide most likely to pose a risk to human health. As reviewed in more detail in the section below, such exposures would be most likely to result in thyroid morbidity as opposed to other forms of illness or disability.

On March 27, 1989, the CDC issued a Request For Proposals (RFP) (Number 200-89-0716 P) to solicit applications from organizations wishing to conduct such an investigation. The proposal submitted by a team of investigators at the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle was selected by the CDC, and a contract was awarded to the FHCRC on September 19, 1989.

B. Ionizing Radiation and Thyroid Disease

Radiation-induced thyroid disease in humans has generally been considered in two broad categories: thyroid neoplasia (benign and malignant neoplasms) and hypothyroidism. More recently, it has been suggested that the risk of autoimmune thyroid disease may also be increased by radiation exposure (28). In addition, acute thyroiditis can occur after high doses of radiation from orally administered ^{131}I in the treatment of certain thyroid disorders, such as thyroid cancer and hyperthyroidism (29). The degree to which the thyroid is ablated by radiation exposure, and the degree to which thyroid neoplasms or hypothyroidism result, is dependent upon several factors: type of radiation, dose, dose rate, age at exposure, sex, and current age. The type of radiation causing such disorders may be classified as either external (primarily gamma or x-radiation) or internal radiation (primarily beta) from radioiodine.

B.1. Thyroid Neoplasia: Exposure to External Photon Radiation

The evidence linking ionizing radiation with the development of thyroid neoplasms in humans has arisen largely from two sources: 1) studies of people who were previously exposed to external radiation in childhood for treatment of benign diseases of the head and neck (30-41); and 2) studies of Japanese survivors of the bombings of Hiroshima and Nagasaki who were exposed primarily to external radiation (42,43). The first category of exposures includes children treated with external radiation for acne, tonsilar hypertrophy, cervical adenitis, fungal infections of the scalp, suspected thymic enlargement (chest), and pertussis (chest). Although the first article describing the use of external radiation as therapy for such problems was published in 1907 (44), it was not until the 1950s that increased rates of thyroid neoplasia in exposed individuals began to be recognized (30-32).

Current evidence suggests that there is a dose level above which radiation-induced carcinogenesis occurs less frequently than at lower doses (45). Animal data and limited human studies collectively suggest that at external radiation doses over 20,000 milligray (mGy) or perhaps 15,000 mGy, cell killing and sterilization reduce the risk of carcinogenesis (32,34,40,41). Thus, estimates of risk for thyroid neoplasia from external radiation are based on doses to the thyroid of less than 15,000 mGy.

Several cohorts exposed in childhood to external gamma radiation have been followed and evaluated for the subsequent development of thyroid neoplasia. An overall summary of such studies is difficult because important factors such as dose, age at exposure, and length of follow-up have differed. Nevertheless, these studies collectively demonstrate a dose-response relationship between external radiation dose and the development of benign thyroid adenomas and thyroid cancers (29). There have been six principal studies involving populations exposed to external radiation (35,46-50). The range of median doses evaluated has been between approximately 60 to 8080 mGy to the thyroid. Estimates of absolute excess risk of thyroid cancer range from 0 to approximately 4 cases per million person-year-rad (PYR), averaging about 2.5 per million PYR. Among people exposed in childhood to external radiation, the absolute excess risk for total thyroid nodules has been reported to be 12.3 excess cases per million PYR (which includes thyroid cancer). A study of Israeli children irradiated for *tinea capitis* revealed higher absolute risk estimates (14 per million PYR) resulting from lower thyroid doses (average 90 mGy; range 43-169 mGy) (35).

Ron et al. analyzed the primary data from seven previously published studies of persons exposed to external radiation (51). These data showed a linear dose-response for individuals developing thyroid cancer if they were exposed before age 15. This linearity was observed down to a dose of 100 mGy but leveled at higher doses greater than 10,000 mGy. For persons exposed in childhood the excess relative risk per Gray (ERR per Gy) was 7.7 (95% confidence interval [CI] 2.1, 28.7) whereas little risk was observed for individuals exposed after age 20.

Studies of Japanese A-bomb survivors, who were exposed primarily to whole-body external radiation, show a similar dose-response relationship for thyroid cancer based on T65DR dosimetry (42).

The latest follow-up of the Japanese cohort confirms a strong dose-response for thyroid cancer. The crude incidence rates (cases per 10,000 person-years) for three dose groups (<10 millisieverts [mSv], 10-990 mSv, and >1000 mSv) showed a marked increase with increasing dose: 1.08 for the comparison group, 1.49 for the low dose group, and 3.71 for the high dose group (43). In addition, a strong linear dose-response was shown with an estimated excess RR at 1000 mSv of 1.15 (95% CI 0.48, 2.14). Age at exposure was a significant modifier of thyroid cancer risk. The excess RR at 1000 mSv was 9.46 (95% CI 4.11, 18.86) for persons exposed under age 10, compared to 3.02 for persons exposed between the ages of 10-19. These results at young ages of exposure contrasted with those for exposure after age 20, for whom the excess RR was 0.10 (95% CI -0.23, 0.75), consistent with no increased risk of thyroid cancer.

B.2. Thyroid Neoplasia: Exposure to Radioactive Iodine

B.2.a. Medical Exposures to Radioiodine

Although animal studies clearly indicate that ^{131}I can induce thyroid cancer (52-54), much less information is available in relation to the induction of thyroid neoplasia in humans from doses due to ^{131}I. Evidence from human populations arises from two principal sources: persons receiving therapeutic (moderately high) doses of ^{131}I for Graves disease or thyrotoxicosis, and persons who received diagnostic (lower) doses for thyroid nuclear ^{131}I scans to evaluate suspected thyroid disease. The early studies of persons receiving therapeutic ^{131}I for hyperthyroidism have shown no convincing evidence that the risk of thyroid cancer is increased among persons receiving ^{131}I (55-58). Most of the participants in those studies were adults at the time of exposure, were followed for very short periods, had existing thyroid disease at the time of treatment, and were treated with radiation doses that were quite high (generally 20,000 - 100,000 mGy).

A long-term follow-up of one of these studies (55) was recently published (59). This study compared cancer mortality rates in patients previously treated with ^{131}I, usually for Graves disease, to expected mortality rates for the general US population. Although no increase in total cancer mortality was found for patients treated with ^{131}I, an increase in the risk of death from thyroid cancer was demonstrated. The standardized mortality ratio (SMR) for thyroid cancer was 3.94 (95% CI 2.52, 5.86). While this increased risk was statistically significant, the absolute numbers of excess deaths were small and the authors suspected that underlying thyroid disease at the time of ^{131}I treatment might have contributed to these results.

Similar results were obtained from another recent study which evaluated cancer incidence and mortality in 7400 patients who were treated with radioiodine from 1950 to 1991 in England (60). The mean age of the cohort was 56 and the mean ^{131}I administered activity was 308 MBq (8.316 millicuries). The incidence and mortality rates were compared to registry data for England and Wales. Overall cancer incidence in the patient cohort was decreased (standardized incidence ratio [SIR] 0.83, 95% CI .77, .90) as was overall cancer mortality (SMR 0.90, 95% CI .82, .98). In contrast, the incidence and mortality of thyroid cancer were increased approximately 3-fold (SIR 3.25, 95% CI 1.69, 6.25 and SMR 2.78 95% CI 1.16, 6.67). However, the absolute numbers of thyroid cancer cases and deaths were quite small and the authors could not distinguish between underlying thyrotoxicosis versus radioiodine as the cause of the increased thyroid cancer incidence and mortality.

A number of studies have evaluated persons exposed to much lower doses (generally 500-1000 mGy) through diagnostic procedures (61-64). Hall et al. (63) reported in 1996 a 40-year follow-up experience of 34,000 patients who had received ^{131}I for diagnostic purposes. The mean dose for this cohort was 1100 mGy. The SIR for thyroid cancer was 1.35 (95% CI 1.05, 1.71). Excess thyroid cancers were apparent only among patients who were originally suspected of having a thyroid tumor, whereas no increased risk was noted for those referred for other reasons (63). In the group referred for suspected thyroid tumors, the increased risk was not related to thyroid dose, age at exposure, or time since exposure. The mean age at exposure of this cohort was 43; although 2408 members of the cohort (7%) were less than

age 20, stratification of risk by very young age was not reported. The authors of this study concluded that the small increase in thyroid cancer was likely due to the underlying thyroid condition and not radiation exposure. The data also suggested that protraction of dose (lower dose rate) might result in lower risk than an acute exposure of x-rays of the same total dose.

In 1989, the Food and Drug Administration's Center for Devices and Radiological Health reported the risk of thyroid disease from diagnostic ^{131}I in a cohort comprised exclusively of children and adolescents (64). Of 3483 children in the exposed group, 48% were less than 10 years and 24% were less than 5 years at time of entry into the cohort. The average length of follow-up was 27 years; the mean and median thyroid radiation dose were both less than 500 mGy. The exposed group and two separate control groups were sent questionnaires inquiring about subsequent thyroid surgery. Of 34 patients with thyroid surgery, 20 were included in the analysis. Among these 20, the proportions with malignant tumors or with benign thyroid conditions were higher in the exposed group than in either control group, however none of these differences was statistically significant (64).

B.2.b. Environmental Exposures to Radioiodine

Until 1990, the principal sources of information regarding the risk of radiation-induced thyroid disease from environmental exposures were limited to studies of Utah schoolchildren and Marshall Islanders exposed to fallout from atmospheric nuclear testing. Since then, a dramatic increase in childhood thyroid cancer has been documented from radiation exposure from the Chernobyl accident in 1986, and additional follow-up data have been published for the Utah cohort exposed to fallout from the Nevada Test Site. In contrast to the medical exposures described above, which were due exclusively to ^{131}I, most of these environmental exposures contained a mixture of ^{131}I, external radiation, and short-lived radioiodines. The following section is a brief summary of studies that have investigated the risk of thyroid neoplasia from environmental exposures to radioiodine.

B.2.b.1. Utah

Over 100 atmospheric nuclear tests were conducted at the Nevada Test Site between 1951 and 1958. Initial studies of thyroid disease incidence in Utah schoolchildren appeared to show no difference in thyroid disease outcomes compared to children from unexposed areas (65,66). However, a follow-up study of this cohort, published by Kerber, et al. in 1993, reported an excess risk of thyroid neoplasms that was associated with exposure to radioiodine from the Nevada Test Site (67).

In that study, a relative risk of 3.4 (95% CI 0.5, 26.9) for the period prevalence of thyroid neoplasms (benign and malignant) during 1965-1986 was observed participants with estimated thyroid doses >400 mGy. A statistically significant excess relative risk of 0.7% per mGy (with 95% lower confidence bound 0.074%) was observed for total neoplasms (benign and malignant). Although positive dose-response trends were noted for total nodules and thyroid cancer (when analyzed separately), these were not statistically significant. Among 3545 study participants for whom thyroid doses could be estimated, the mean dose was 98 mGy, although for those who were children in the most heavily contaminated study county (Washington County, Utah), the mean dose was about 170 mGy. Although the dose was reported to be primarily from ^{131}I, the contribution of external radiation or short-lived radioiodines is uncertain. The authors report that the study conclusions were limited by small numbers of exposed individuals and a low incidence of thyroid neoplasms.

B.2.b.2. Marshall Islands

Of the 66 atomic tests conducted in the Marshall Islands between 1946 and 1958, the BRAVO thermonuclear test on March 1, 1954 produced the largest single radiation exposure to the Marshallese people. Extensive evaluation of this population by Brookhaven National Laboratory has shown an increase in benign and malignant thyroid nodules in residents of the northern atolls of Rongelap and Utirik (68,69).

Thyroid doses have been estimated to be primarily from a mixture of the short-lived radioiodines (^{132}I, ^{133}I, ^{135}I) and to a lesser extent, ^{131}I and external gamma radiation (70,71). For thyroid nodules, the absolute excess risk coefficient for Marshallese people from Rongelap and Utrik was reported to be 830 cases per Gy per million persons per year, or 8.3 cases per million PYR (71).

A more recent update by the Brookhaven group showed little change in prevalence of thyroid nodularity among Rongelap and Utrik residents (72). These authors also reviewed prior estimated thyroid doses in the exposed persons. For the Rongelap group, the estimated mean dose was 25,630 mGy for those with benign nodules and 16,300 mGy for those with malignant disease. For the less exposed Utrik group, the estimated mean dose was 3710 mGy for benign nodularity and 2780 mGy for malignant disease.

Although the Brookhaven studies have maintained that fallout exposure from the BRAVO test affected only the atolls Rongelap and Utrik, additional dosimetry studies have suggested a much wider area of fallout exposure (73-76). In addition, a retrospective cohort study of over 7000 Marshall Islanders showed that the prevalence of palpable thyroid nodularity (≥ 1.0 cm) decreased linearly with increased distance from the Bikini test site (77). These results were highly statistically significant and strongly suggested that fallout radiation affected a much wider region of northern and central atolls, including those with populations used by Brookhaven as controls. A new absolute risk coefficient of 1100 excess cases of thyroid nodules per Gy per million persons per year (11 cases per million PYR) was calculated using a revised estimate of the prevalence for unexposed Marshall Islanders (77). These authors also concurred with others that the exposure to the BRAVO test fallout (reported to be primarily short-lived radioiodines) appeared to be nearly as effective as external radiation in producing both benign and malignant thyroid neoplasms (68,71,77).

The authors of a recent report (74) attempted to independently assess the prevalence of thyroid nodularity in the Marshall Islanders, and to compare their results to the 1987 study described above. They reported a much higher prevalence of thyroid nodules in the population and a relationship between thyroid nodules prevalence and distance to Bikini atoll which was only of borderline statistical significance. However, the apparently increased prevalence can be explained in part by the inclusion of ultrasound abnormalities along with palpable nodules in their criteria for thyroid nodules. Also, since they screened very small numbers of persons from each atoll in the Marshall Islands, their study had little statistical power to detect a relationship between thyroid nodule prevalence and distance from the Bikini test site. Therefore their results cannot be viewed as inconsistent with the earlier reports.

B.2.b.3 Chernobyl

Beginning in 1992, articles began to appear reporting increased rates of thyroid cancer in children who were exposed to radiation from the Chernobyl accident in April of 1986 (78,79). Marked increases in childhood thyroid cancer have since been reported for areas surrounding the Chernobyl reactor especially in Belarus and Ukraine (80-82). Pacini et al. evaluated thyroid cancer cases reported from registries in Belarus since 1986 and compared them with presumably unexposed cases reported from registries in France and Italy (80). Of 472 cases of thyroid cancer from six regions in Belarus, 52% were from Gomel, the most heavily contaminated region of Belarus; the numbers of cancer cases throughout Belarus roughly correlated to the degree of radioactive contamination. In addition, the Belarussian cases, when compared to the French and Italian cases, were younger and more likely to have cancers that were aggressive at initial presentation and papillary in histology. Correlations of population rates with population measures of radiation dose (e.g. collective dose) have been reported in Ukraine and Russia as well (83). Increased rates of thyroid cancer among those who were young at exposure have also been reported in Ukraine (84) and Russia (85).

Despite considerable efforts to assess the occurrence of thyroid cancer after the Chernobyl accident, and to determine to what extent changes in occurrence since the accident are due to radiation exposure, there is very little published information assessing a dose-response relationship between Chernobyl radiation exposure and thyroid cancer based on individual estimates of radiation dose to the

thyroid. A recent report by Astakhova et al. (86) is probably the best attempt to date, but individual doses to children were nevertheless inferred from village Cs-137 measurements. Based on 107 cases under age 15 at the time of the accident, a strong relationship was found between estimated thyroid dose and the risk of thyroid cancer.

The radiation exposure received by people living near Chernobyl was in large part due to ^{131}I, although external radiation as well as short-lived radioiodines also contributed to the dose. Several dose reconstruction efforts have published representative thyroid dose estimates that span a wide range. Stepanenko et al. reported thyroid doses for the heavily contaminated regions of Bryansk Oblast ranging from 1600 to 2800 mGy for infants less than 1 year, and 1000 to 1800 mGy for children age 3-6 years (87). Gavrilin et al. reported estimated average thyroid doses for 14 exposed territories in Gomel and Mogilev which ranged from 220 mGy to 4700 mGy for children up to 7 years and 150 mGy to 3100 mGy in children up to 18 years (88). Likhtarev and colleagues reported estimated thyroid dose distributions in persons from five oblasts in Ukraine which showed that almost 90% of the doses in children up to age 7 were between 5 and 1000 mGy (89).

Thus, although there is now compelling evidence that the radiation exposures from Chernobyl have increased the risk of thyroid cancer in children in contaminated areas, and it is possible to estimate the range of thyroid doses received by populations in those areas, at present there is little quantitative information based on individual dose estimates regarding the risk of radiation-induced thyroid cancer after the Chernobyl accident. Furthermore, few studies have adequately addressed the potential for other factors such as iodine deficiency to modify the risk of radiation-induced thyroid cancer from Chernobyl.

B.2.c. Relative Biological Effectiveness of ^{131}I in the Induction of Thyroid Cancer

The lack of clear human evidence regarding ^{131}I induced thyroid neoplasia makes it particularly difficult to estimate the relative biological effectiveness of ^{131}I compared to external radiation in the induction of thyroid cancer. The National Council on Radiation Protection (NCRP) has reviewed data from many animal studies which have suggested that ^{131}I is from 1/2 to less than 1/20th as effective as external radiation in inducing thyroid cancer (45). One study showed that ^{131}I was equally effective to external radiation in causing thyroid cancer in Long Island rats although the effect was dependent on the presence of increased TSH stimulation (54). Based on human experience, the relative biological effectiveness was thought to be between zero and one-half. In reviewing the results of both animal and human studies, the NCRP suggested in its 1985 report that ^{131}I is one-third as effective as external radiation in producing thyroid cancer in the general population (45). It should be noted that this was intended by NCRP as a conservative value for radiation protection standards as opposed to risk estimation. The BEIR V report suggested that the radiation dose from internally deposited ^{131}I may be two-thirds as effective as external photon irradiation (90). A new NCRP report on this issue is expected but is not published at the time of this writing.

Several factors may be important in explaining a differential effect of ^{131}I as a carcinogen relative to external radiation. These factors include dose rate and the relative heterogeneity of the distribution within the thyroid gland of the dose from ^{131}I, compared to the more homogeneous dose from external radiation. Although information is limited, several studies suggest that protraction of the exposure with reduction of the dose rate may decrease the risk of developing thyroid cancer. As noted above, Hall et al. (63) suggested that the lack of radiation effect they observed in persons receiving diagnostic doses of ^{131}I may be related to the lower dose rate of ^{131}I, since the dose from a single administration of ^{131}I is delivered over a 6 week period. They speculated that this may be sufficient time for DNA repair to occur. Ron et al. also examined the effect of external radiation dose fractionation on the risk of developing thyroid neoplasia (51). They pooled the results of three studies that included fractionated exposures and found a 30% reduction in excess relative risk (ERR) per Gy for persons whose total dose was accumulated over 2 or more exposures.

One additional study has specifically examined the effect of dose rate in children who were given external radiation for skin hemangiomas. A total of 396 children were examined at a mean of 22 years after receiving radiation in infancy (mean total dose 86 mGy) for either a short duration (seconds to a few minutes) or longer duration (30 minutes to several hours). The risk of developing a thyroid nodule increased with total dose and appeared to be linked to doses that were delivered in short duration. Although no correlation with dose was found for children exposed for only long duration, the correlation with dose for short duration approached, but did not achieve, statistical significance (ERR per Gy=10, $p<0.2$) (91). These authors suggested that dose rate may play a role in the risk of developing thyroid neoplasia from external radiation exposure.

B.3. Hypothyroidism

External ionizing radiation to the thyroid has been documented to induce hypothyroidism, although generally at high doses. Maxon reviewed a number of studies which found no clinical hypothyroidism in people who were followed up to 24 years after exposure to doses up to 10,000 mGy to the head and neck (29). This review also included data on people receiving high doses of external radiation who developed hypothyroidism. These were typically case reports or series of patients receiving radiation therapy for malignancies such as lymphoma. Although the data are limited, the authors concluded that the induction of hypothyroidism from external radiation was likely only at doses above 10,000 mGy.

More information is available regarding the risk of hypothyroidism following radioiodine exposure. Maxon reported the risk of hypothyroidism in 6000 patients given a single dose of ^{131}I for the treatment of hyperthyroidism (29). A strong linear dose-response between thyroid dose and the probability of hypothyroidism at five years after treatment was observed. The dose range was 25,000 mGy (minimum dose) to 200,000 mGy. The probability of hypothyroidism was 50% at five years for persons treated with 200,000 mGy of ^{131}I. These data suggested that at the minimum treatment dose of 25,000 mGy, the probability of hypothyroidism was approximately 15% at five years. It should be noted that the risk of hypothyroidism from ^{131}I in patients with Graves disease may not be generalizable to the general population.

Hypothyroidism was among the disease outcomes investigated in the Utah Study (92). The period prevalence of hypothyroidism during 1965 through 1986 tended to decrease with increasing estimated dose. The relative risk for those with estimated doses > 400 mGy was 0.3 (95% confidence interval 0.0, 2.2), thus providing no evidence that exposure to fallout from the Nevada Test Site was associated with in increased risk of hypothyroidism.

B.4 Autoimmune Thyroiditis

Two recent studies have suggested that exposure to ionizing radiation may be associated with an increased risk of autoimmune thyroiditis. In a follow up of the Nagasaki Adult Health Study cohort of Japanese A-bomb survivors, the dose-response relationship between the prevalence of autoimmune hypothyroidism and radiation exposure was evaluated. Autoimmune hypothyroidism was defined as any TSH elevation with positive thyroid autoantibodies. Either a positive anti-microsomal antibody or positive anti-thyroglobulin antibody was considered a positive result. A dose-response was reported for antithyroid antibody positivity in persons with spontaneous hypothyroidism (28). This result suggested that exposure to external radiation might be a risk factor for developing autoimmune thyroiditis with hypothyroidism. However, the published report provided very limited information, showing only a linear-quadratic dose-response that was described as significant at the 5% critical level.

A similar result was observed in children exposed to Chernobyl fallout radiation (80). Of 171 Belarussian children, 46% had positive anti-TPO levels compared to 23% of 103 children from Italy.

Higher levels of anti-thyroglobulin were also seen in the Belarussian children compared to the Italian children. The authors postulated that thyroid autoimmune reactions may be related to radiation exposure.

Although additional data are needed to confirm an association of autoimmune thyroiditis with radiation exposure, one can speculate about potential mechanisms. One question would be whether radiation might be triggering an autoimmune response having the same natural history as spontaneous autoimmune thyroiditis with the propensity toward developing hypothyroidism. Alternatively, radiation might be causing a secondary, nonspecific autoimmune reaction resulting from damage to thyroid tissue.

C. Ionizing Radiation and Parathyroid Disease

Although the primary purpose of the HTDS was to determine whether thyroid disease is increased among persons exposed to radioactive iodine released from Hanford, a secondary objective was to determine whether persons exposed to radioactive iodine from Hanford are at an increased risk of developing hyperparathyroidism. Because the parathyroid glands are located close to the thyroid, it is possible that they may receive a radiation dose from beta-emitting ^{131}I taken up by adjacent thyroid cells. In considering potential health effects associated with thyroid radiation exposure, it may therefore be important to include effects on the parathyroid glands.

C.1. Hyperparathyroidism: Exposure to External Photon Radiation

There is considerable evidence to support the association between hyperparathyroidism and prior head and neck exposure to external beam photon radiation. Since the first case report of hyperparathyroidism in an individual exposed to head and neck radiation by Rosen, et al. in 1975 (93), there has been increasing evidence to indicate that ionizing radiation is a risk factor for the development of hyperparathyroidism.

In addition to several retrospective studies, Tisell et al. (94) reported that 14% of 444 persons who were previously treated with x-rays for tuberculous neck adenitis subsequently developed hyperparathyroidism (HPT) at least 24 years after treatment. A statistically significant dose response was found for developing HPT (dose range 0.6-45.7 Gy). For persons with doses greater than 14 Gy, 29% developed HPT with a relative risk in women twice that of men.

Cohen et al. (95) have extended their investigation of hyperparathyroidism in individuals exposed to head and neck radiation in childhood. In such persons, who had received a mean dose of approximately 8000 mGy to the tonsilar region before the age of 16, the incidence of clinical hyperparathyroidism was 18.7 per 100,000 person-years below the age of 40 and 171 per 100,000 person-years in the age range of 40 to 60 years. This represented a 2.9-fold and a 2.5-fold increase, respectively, in the incidence of hyperparathyroidism compared with that in the general population. Of interest, the above authors also found that in those persons developing hyperparathyroidism, 31% also developed thyroid cancer, compared to only 11.2% of individuals who had received prior radiation therapy but did not develop parathyroid tumors. The mean latency was 34.7 years with a maximum latency of 46 years. In addition, 90% of the cases of hyperparathyroidism were secondary to single parathyroid adenomas. In the latter study the authors recommended screening calcium measurements in the routine evaluation of persons with a prior history of childhood radiation treatments to the head and neck.

In an extension of the above study which compared prevalence rates with general population rates, Schneider et al. have more recently examined the dose-response relationship for their cohort. They report an excess relative risk of hyperparathyroidism of 0.11 per centigray in a dose range up to 100 cGy (1000 mGy) (96). The authors used dose estimates established for the thyroid; these were used as estimates of the average dose to the parathyroids.

A study of hyperparathyroidism among atomic bomb survivors in Japan corroborates the above results (97). The prevalence of hyperparathyroidism was found to be increased in individuals exposed to 500-1000 mGy when compared to unexposed control persons. A dose-response with a linear trend was observed as well as an age effect, with younger persons having higher risk.

C.2. Hyperparathyroidism: Exposure to Radioactive Iodine

Although the relationship between external beam radiation and the risk of hyperparathyroidism is reasonably well established, there is little evidence to support the existence of a relationship between radioactive iodine exposure and risk of parathyroid tumors. Animal studies have indicated that parathyroid hyperplasia or adenomas develop more frequently in rats given ^{131}I than in control animals. In addition, such studies have also suggested an age effect in rats. A higher frequency of parathyroid tumors has been observed if ^{131}I was given in the first two days of life compared to^{131}I given at 2-4 months of age (98,99).

In a retrospective report, Bondeson et al. (100) reported 600 consecutive cases of primary hyperparathyroidism of whom 10 had documented histories of prior ^{131}I treatment. Such treatment had been given for either Graves Disease or for ablation of thyroid remnants. Age at the time of ^{131}I therapy ranged from 21 to 72 years with the interval to detection of hypercalcemia ranging between 3 and 27 years. These authors also indicate that parathyroid adenomas developed at the sites of thyroid remnants in cases with ^{131}I ablation after thyroid tumor operations.

While the mechanism of parathyroid tumor induction in individuals exposed to external beam radiation is almost certainly due to direct photon beam exposure, the mechanism of postulated parathyroid tumor induction from radioactive iodine is less certain. The parathyroid glands are not known to take up iodine. However it is plausible that parathyroid cells can be exposed to beta radiation from ^{131}I taken up in thyroid cells adjacent to the parathyroid glands. This mechanism of exposure is consistent with the results summarized above since the parathyroid glands in rats are imbedded within the thyroid tissue whereas in humans they exist as separate organs. Although the number of cases is quite small in the study by Bondeson et al. (100), the development of parathyroid adenomas near the site of thyroid remnants treated with ^{131}I supports this hypothesis.

Estimated doses to the parathyroid glands can be calculated if the thyroid dose from radioactive iodine is known. For example, a 5.0 mCi administration of ^{131}I would be expected to give a thyroid dose of approximately 45,000 mGy and a parathyroid dose of approximately 16,500 mGy (101). Therefore, the parathyroid dose from ^{131}I is approximately 30% of the thyroid dose for a given amount of ^{131}I.

Thus, while it seems clear that external radiation is a risk factor for the development of parathyroid tumors and subsequent hyperparathyroidism, the association of parathyroid disease with radioactive iodine exposure is less certain. Nevertheless, the available data are suggestive and warrant further investigation.

D. Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

Since the mid-1980s, high-frequency ultrasound has increasingly been used in the evaluation of thyroid nodules. Although the traditional definition of a thyroid "nodule" is based on clinical palpation, the greater sensitivity of ultrasonography has led to its greater use, since it can detect nonpalpable, millimeter size abnormalities. Several important issues, however, have arisen with the use of this technology: 1) thyroid UDAs have been shown to occur frequently in the general population without good understanding of their risk of malignancy or biologic significance; 2) thyroid UDAs have often been classified as "nodules" regardless of size; 3) the use of ultrasound in defining criteria for thyroid nodules has made it difficult to compare clinical thyroid outcomes among epidemiological studies using different criteria for thyroid nodularity and; 4) although ultrasound has exceptional sensitivity, recent data regarding specificity (the ability to distinguish benign from malignant nodules) suggest that the increased specificity of ultrasonography is associated with a significant decrease in sensitivity.

As described further below, a few published studies have examined the possibility of association between radiation exposure and thyroid UDAs. However, to interpret those studies properly, careful attention must be paid to the issues mentioned above. The following section summarizes the published literature regarding the prevalence, clinical significance, and possible radiogenesis of thyroid UDAs.

D.1 Prevalence of Thyroid UDAs

A number of studies have shown a high prevalence of thyroid UDAs in the general population. Tan et al. recently reviewed the literature and reported a range of prevalence of 17-67% (102). In 1000 persons referred for evaluation of hypercalcemia (of whom 8% had a nodular goiter), 46% had discrete thyroid lesions on ultrasound and 38% were reported to have thyroid nodules (103). While these patients are unlikely to be representative of the general population, they were not referred for suspicion of thyroid disease. The highest prevalence of thyroid UDAs was reported in a prospective study of 100 female employees responding to a notice on a bulletin board: 67% of these women, mean age 43, had abnormal thyroid ultrasound scans (104). The results of this study are limited by small numbers. Thyroid UDAs in populations without apparent thyroid disease have also been documented outside the US with prevalence figures ranging 17-27% (105-107). Most of these studies have been consistent in showing that nonpalpable thyroid UDAs are generally small and that solitary nodules on clinical examination are often associated with multiple other thyroid UDAs. Both Tan (108) and Brander (105) have demonstrated that 48% of patients with known palpable thyroid nodules greater than 1 cm harbored additional thyroid nodules found on ultrasound.

Brander and colleagues have published two important studies. In the first study, 253 persons randomly selected from a Finnish city council registry were screened for thyroid UDAs (109). The sample was distributed evenly among four age brackets from 20 through 50. The community was not thought to have endemic goiter. Thyroid UDAs were detected in 69 persons (27%). These abnormalities were solitary in 57%, multiple in 22%, and diffuse in 22%. The mean age for persons with normal ultrasound scans was 35, the mean age for the group with abnormal ultrasound findings was 37. The frequency of these abnormalities was higher in women than men and increased with age for both sexes. For women, the prevalence of thyroid UDAs was 30% in the 20-29 age group, 32% in the 30-39 age group, and 41% in the 40-50 age group. All participants underwent thyroid palpation prior to ultrasound examination. Palpable abnormalities were detected in 13 persons (5.1%): three with a solitary nodule, five with multiple nodules, and five with abnormal consistency. Fine needle aspirations were done in 30 individuals. All were negative for malignancy with one intermediate probability of neoplasm; that person underwent surgery and had a follicular adenoma. The authors commented that thyroid UDAs were common in an unselected population, and that the likelihood of malignancy was low. They recommended a conservative approach to these lesions.

In the second study (110), Brander and colleagues performed follow-up ultrasound scans in persons who initially had thyroid UDAs in the previous study. Of the 69 persons with initial thyroid UDAs, 57 (83%) were located and re-evaluated 5 years later. Of these 57 persons, 28 had thyroid UDAs that were defined as macrofollicles (lesions less than or equal to 5mm). After 5 years, 14 macrofollicles were unchanged, 5 increased in size, 5 decreased in size, and 4 had no follow-up.

The remaining 29 persons had a total of 34 nodules which had been detected during the initial ultrasound screening. Of these, 12 had grown over 5 years, 8 had either disappeared or diminished in size, and in seven persons a new lesion developed. Of the 12 that had grown, biopsy was performed in 10 with 9 benign results and 1 which was a benign adenomatous nodule after surgical excision. Of the 7 new lesions, biopsy was performed in 5 and all were benign. At the end of the 5-year follow-up, there were no individuals with thyroid cancer who previously had thyroid UDAs at the initial screening. The authors acknowledged the small size of their study but concluded that in contrast to persons with nodules selected for surgery, "most lesions randomly detected at ultrasound of the thyroid are benign."

Bruneton evaluated 1000 healthy volunteers without history of thyroid disease and performed high frequency thyroid ultrasound examinations (111). Although selection criteria or mean age were not provided, 57% of participants were over 50 years. Ultrasonography was performed with 13 MHz transducers and all ultrasound nodules greater or equal to 3 mm were counted. One or more nodules were detected in 34.7% of participants. For persons less than age 50 (n=431), the prevalence was 25%. For persons greater than age 50 (n=569), prevalence was 42%. For all ages, the prevalence in women was 44% and the prevalence in men was 17.7%.

A Belgian study assessed thyroid UDAs in 300 patients who were referred for abdominal ultrasound examinations (107). Although this study sample is not a random representation of the general population, there were extensive exclusion criteria for those with symptoms or signs of thyroid disease. The mean age was 47 (1-88) and 55% of participants were males. Small echoic nodules were found in 19% of patients. In patients in their 7th decade, the prevalence increased to over 40%.

These ultrasound prevalence studies can be compared to the autopsy study by Mortensen in 1955 which showed that approximately 50% of 1000 consecutive autopsies had single or multiple thyroid nodules in glands which appeared "clinically normal" (112).

D.2. Specificity of Thyroid Ultrasonography in Predicting Thyroid Cancer

There has been significant controversy regarding whether there are ultrasound characteristics that can independently predict malignancy in thyroid lesions. Rago and colleagues assessed 104 consecutive patients by conventional ultrasound and color flow doppler prior to thyroid surgery (113). The characteristics of the halo sign, hypoechogenicity, and microcalcifications were assessed by conventional ultrasound while Type I, II, and III color flow patterns were assessed by color doppler. The combination of absent halo, the presence of microcalcifications, and a Type III color flow pattern increased specificity for thyroid cancer to 97%. However, the sensitivity decreased to only 16%. Thus, while ultrasound and color flow doppler increased the specificity for thyroid cancer it did so at the expense of sensitivity for predicting thyroid cancer.

Takashima studied the sonographic and pathologic correlation in 69 of 99 surgically removed nodules (114). Microcalcification showed the highest specificity of 93% with a positive predictive value of 70% for thyroid cancer. However, the sensitivity was only 36%. They discussed the distinction between dense calcifications, which are found in both thyroid cancer and benign lesions, and microcalcifications which are much more specific for thyroid cancer. However these are not always seen on ultrasound but may be found on pathology review. The authors conclude that "none of the various sonographic features, such as multiplicity of nodules, presence or absence of halo or cystic areas, lesion echogenicity, or margin

characteristics help to reliably distinguish between benign and malignant thyroid nodules." They state that "microcalcifications were useful however sonographic microcalcification is not a sensitive nor sufficiently accurate indicator of malignancy because pathologic microcalcifications are found, at most, in only 60% of thyroid cancers."

Tominori evaluated the combination of ultrasonographic and cytologic characteristics in predicting thyroid cancer and developed an index which prepared patients better for selection for thyroid surgery. He acknowledged that "clearly sonographic features alone do not reliably separate benign from malignant thyroid nodules" (106).

In a similar statement, Sakaguchi reported that studies indicate that several ultrasound characteristics are "suggestive" of thyroid cancer such as solid and hypoechoic lesions, irregular margin, and fine microcalcifications (115). However, the authors stated that, "There is no single sonographic criterion that distinguishes benign from malignant thyroid nodules." In a recent commentary, Hegedus and Karstrup state, "A general finding – has been that there is no US [ultrasound] pattern, alone or in combination with other techniques, that may be considered specific for thyroid cancer" (116).

D.3. Ionizing Radiation and Thyroid UDAs

The increased sensitivity and the development of portable ultrasound equipment have made ultrasonography particularly attractive in evaluating abnormalities of the thyroid gland in persons exposed to environmental radiation. In contrast to the increasing volume of literature regarding thyroid UDAs in the general population, much less is known about whether ionizing radiation causes an increase in thyroid UDAs prior to the development of clinical disease.

Schneider and coworkers evaluated a subgroup of their Michael Reese cohort who had been exposed to head and neck radiation therapy during childhood for benign conditions. They selected 54 individuals who had previously had normal thyroid exams and normal thyroid nuclear scans in the 1974-76 time period. Of these 54 persons in this follow-up study many years after exposure, 47 (87%) had one or more discrete thyroid UDAs (117). In this cohort, external radiation exposure was clearly associated with increased thyroid UDAs. The authors concluded that: 1) thyroid nodules continued to develop in radiation-exposed individuals many years after exposure and 2) although thyroid UDAs were quite common in the general population, they were more prevalent in radiation-exposed populations.

Other studies have also suggested that thyroid UDAs are more common in exposed populations. Antonelli, et al. compared ultrasound scans of two groups: 50 hospital workers with occupational radiation exposure (external radiation) in a hospital setting and 100 controls without such exposure (118). Thyroid UDAs were detected in 38% of the exposed persons and only 13% of the controls. Similarly, Sugenoya and colleagues (119) compared 299 children who were exposed to Chernobyl radiation to 323 children who were unexposed. Although none of the children in either group had palpable abnormalities, 34 of the exposed (11.4%) had thyroid UDAs compared to 4 unexposed children (1.2%).

There is very limited information regarding the dose-response relationship between radiation exposure to the thyroid and thyroid UDAs. While such abnormalities might be expected to correlate with clinical thyroid disease, the question of whether thyroid UDAs might represent an early marker of radiation injury prior to the development of clinical disease is unknown. There are currently no studies in the literature to answer this question.

III. STUDY OBJECTIVES

The primary objective of the HTDS was to determine whether thyroid morbidity (including, but not limited to hypothyroidism, benign neoplasia, and malignant neoplasia) is increased among persons exposed to atmospheric releases of radioactive iodine from the Hanford Nuclear Site between 1944 and 1957. If an effect was detected, the study was designed to further determine in what way the increase in thyroid morbidity is related to the dose of radiation received (i.e., the characteristics of any dose-response relationship).

In addition to these primary objectives, the HTDS had three specific secondary objectives: 1) to determine whether hyperparathyroidism is increased among persons exposed to the Hanford radiation releases and who received radiation doses to the thyroid and, if so, to determine in what way the increase in hyperparathyroidism is related to the dose of radiation received; 2) to provide information to residents of the communities surrounding the Hanford Site regarding the objectives, design, and conduct of the study, as well as the findings and results of the research; and 3) to assess the appropriateness of the methods employed and the degree to which such an investigation could be successfully planned and executed, given the long interval since exposure and the uncertainties regarding radiation dose.

IV. STUDY DESIGN

A. Eligibility Criteria

The HTDS was based on a cohort of people defined by the following eligibility criteria:

- Mother's residence at the time of the participant's birth: Benton, Franklin, Walla Walla, Okanogan, Ferry, Stevens, or Adams County in Washington State
- Year of birth: 1940 – 1946.

The rationale for this choice of counties and years is described in sections IV.A.1 and IV.A.2 below. The mother's usual residence at the time of the participant's birth, which can be determined from birth records, was used as a criterion since it was likely to indicate the participant's place of residence during the first years of Hanford's operations, when the largest releases of ^{131}I occurred (see section V.A.2 below). The cohort included the majority of the possible combinations of the seven counties and seven birth years. However, birth year subcohorts for certain counties were not included since they were unlikely to include many participants with relatively high thyroid radiation doses (see sections V.A.2 and V.A.3 below).

A.1 Mother's Residence at the Time of the Participant's Birth

Geographical proximity to the Hanford Nuclear Site is clearly a determinant of radiation doses received by area residents. The atmospheric transport and deposition of radioactive materials depend on the location of the source of the release, the surrounding topography, and meteorological conditions at the time of the release (i.e., wind speed, wind direction, precipitation and atmospheric stability). The HEDR Project considered such factors to estimate the atmospheric dispersion of radioactive iodine from Hanford. Preliminary HEDR results were used to define the geographical boundaries for selection of the HTDS Pilot Study Sample, and final HEDR estimates used to refine the boundaries for the selection for the Transition and Full Study Samples. The 75,000 square mile geographical domain within which the final HEDR model applies is shown in Figure II.A-1 above.

The prevailing winds in the vicinity of the Hanford Site blow primarily from the North, Northwest, and West across the Site to the East and Southeast. Although there were some seasonal variations according to month of the year, this pattern was generally consistent throughout the year during the 1940s (120-149). Wind direction determines the directions in which airborne plumes of radioactive material most likely traveled, and thus the geographical areas most likely to have received deposits of radionuclides. For the most part, atmospheric releases traveled to areas East and Southeast of the Hanford Site.

Utilizing meteorological data from the 1980s, information regarding the amount of material released, and limited off-site monitoring data, the HEDR Project calculated ^{131}I concentrations in vegetation surrounding the Site. Later calculations conducted by Battelle Pacific Northwest Laboratories using 1944-1947 meteorological data generally confirmed this geographical pattern of ^{131}I concentration in sagebrush. These data suggested that the areas of highest concentration were primarily those closest to the Site to the East and Southeast (e.g., in Benton, Franklin, and Walla Walla counties). Final estimates from the HEDR Project revealed a wider dispersion of ^{131}I, with decreased concentrations in the areas nearest the site and increased concentrations in areas somewhat more removed especially northeast of Hanford. This finding prompted the inclusion of Adams County in the Transition and Full Study Samples.

An important pathway of radioactive iodine exposure in humans is the ingestion of milk produced

by animals grazing on radioactive iodine-contaminated vegetation. Therefore, milk distribution routes and milksheds are also important in defining a geographic area in which people were exposed to radioactive iodine. In an effort to describe such components of a milk pathway for radioactive iodine, the HEDR Project attempted to reconstruct the following types of information for the period of highest releases (150): 1) types, quantities, and sources of feed for dairy cows in the area; and 2) location, relative size, and distribution routes of all fresh milk processors/distributors in the area.

For purposes of planning the Pilot Study, it was important to know the sources and distribution patterns of the milk consumed in the areas of interest during the time period under study. The HEDR Project developed a summary measure for each of the ten counties surrounding the Site, based upon production and consumption data, to indicate whether the county recorded a milk surplus, a milk deficit, or was in relative balance regarding milk production and consumption.

Several important findings were reported (150). Overall, the 10-county area surrounding Hanford was self-sufficient in milk production and, in fact, recorded a surplus of almost 20% in 1945. There is considerable variability by county, however, which is largely explained by different amounts of irrigated pasture available for raising dairy herds. For example, Yakima, Kittitas, and Klickitat counties were milk surplus counties, particularly Yakima and Kittitas. Essentially all of the milk consumed by residents of these counties was produced locally. Similarly, all of the milk consumed in the Walla Walla area was locally produced. In contrast, Benton and Franklin counties imported milk. Two of the primary sources of commercial milk for residents of these counties were the Carnation Dairy in Sunnyside and the Twin City Creamery in Kennewick. Although the Twin City Creamery itself was located in Benton County, it received milk from a number of dairies outside the county.

In addition, two special circumstances with regard to milk supply needed to be considered in selecting potential study participants. First, much of the commercial milk consumed by Richland residents is thought to have come from the Carnation Plant in Sunnyside. In fact, the Atomic Energy Commission had a contract with Carnation in Sunnyside to supply the town of Richland with their milk during this time period (151). Second, a substantial amount of the milk consumed by people living in rural areas (which constituted much of the area during the 1940s) was supplied by backyard cows. It is estimated that between 40% and 90% of the milk consumed by rural families came from this source.

Thus, based upon these preliminary findings regarding meteorological conditions, the deposition and concentration of radioactive iodine in vegetation, and the patterns of milk production and consumption by county, the area encompassed by Benton, Franklin, and Walla Walla counties was defined in the Pilot Study as the area within which people with the highest thyroid doses were most likely to be identified. Adams County replaced Walla Walla County in the Full Study selections, as noted in section V.A.3.b, due to the findings of the HEDR Project's final report.

On July 12, 1990, the HEDR Project released its preliminary or 'Phase I' estimates of thyroid doses potentially received by residents in a 10-county area surrounding the Hanford Site (23). These estimates were based upon computer models that included information regarding the amount of radioactive material released, the dispersion and deposition of the material, the uptake of the material into the food chain, the geographical distribution of food products (especially milk and dairy products), and the consumption of contaminated food products by humans. These preliminary estimates confirmed that people who lived closest to the Hanford Site, particularly to the East and Southeast, were likely to have received the highest radiation doses to the thyroid.

To determine whether thyroid disease is increased among people who received a radiation dose to the thyroid from Hanford radioactive iodine releases, it is necessary to compare rates of thyroid disease among people with different levels of exposure, including very low exposures or no exposure. The considerations described above guided the definition of a group likely to have received the highest doses. However, the selection of groups likely to have little or no exposure, or intermediate levels of exposure, is equally important in properly evaluating whether the radiation exposure is associated with an increase in

the risk of thyroid disease. The most important considerations in defining these groups are: 1) that the groups are comparable to the high-dose group with respect to other factors which could confound any relationship between radioactive iodine exposure and thyroid disease (e.g., geography, urban/rural composition, occupational factors, socioeconomic factors, age, ethnicity, sex); and 2) that the same opportunities and resources exist to identify and trace people in low- and intermediate-dose groups as in the high-dose group.

With these requirements in mind, three types of comparisons can be considered for use in a cohort study of this type. First, rates of thyroid disease in a general population (e.g., the entire United States) could be used to evaluate whether the rates of thyroid disease observed in the cohort receiving a dose are higher than would be expected based upon general population experience. In the present context, however, this approach is problematic primarily because, with the exception of thyroid cancer, incidence rates for the thyroid diseases under study are generally not available for other populations (e.g., the United States or Europe). Estimates could be obtained from other study cohorts that have been followed subsequent to exposure to ionizing radiation (e.g., the New York tinea capitis study), but such rates do not reflect general population experience and the degree to which they can or should be generalized to the eastern Washington experience is questionable.

A second approach would be to include people who received zero or very low thyroid dose in the cohort selected from the geographical areas most likely exposed to the Hanford releases as a comparison group, and to compare disease rates in people with higher dose levels to the rates among those in this "baseline" category. An "internal" comparison group such as this has a number of advantages. Most importantly, concerns regarding comparability of other factors that might influence the risk of thyroid disease are largely resolved. Second, it is more efficient to enroll and study a single cohort, rather than two geographically separate sub-cohorts (one from areas most likely exposed and one from areas most likely unexposed). Third, this approach allows for a very flexible analysis based on both a simple dichotomy of exposure (dose vs. zero or very low dose) as well as a quantitative estimate of dose (i.e., a dose-response). For this approach to succeed, however, relatively accurate individual doses need to be available, a full range of doses needs to be represented in the cohort (or at least a sufficient number of people with relatively high doses), and an adequate number of people with zero dose need to be included.

In this study, particularly for its pilot phase, it could not be assured that the dose distribution in the sub-cohort selected from Benton, Franklin, and Walla Walla counties would allow for such an approach (e.g., that there would be an adequate number of people with very low doses, as well as a full range of higher doses) because the selection of potential study participants could not be based on estimates of an individual's radiation dose. In fact, it could not even be assured at the time the Pilot Study was initiated (1992) that an adequate individual-level dose estimation system would be available from the HEDR Project for this study. Finally, among people born in Benton, Franklin, and Walla Walla counties during 1942-1946, those who received very low doses could not be presumed to be comparable, with respect to their natural risk of thyroid disease, to those who received higher doses. Those with little or no dose would likely have drunk little or no milk, moved to locations more distant from Hanford before accumulating more dose, and drunk milk imported from a less-exposed area. These characteristics may be related to health or socioeconomic status, and while none of them is known to influence the risk of thyroid disease, the possibility that they may could not be ignored.

Consequently, a third approach for identifying comparison participants was to select people who were not likely to have been exposed to the Hanford radiation releases and who were, therefore, not likely to have received a radiation dose to the thyroid, on the basis of geographic proximity to the Hanford Site. The primary purpose of such an approach was to be able to identify potential study participants with a high degree of certainty that they received a very low or no radiation dose from radioactive iodine from Hanford. The two principal concerns with this approach, however, were: 1) to establish that such people were truly unexposed (and, therefore, received very low or zero dose) and 2) to assure that such people are comparable to those who did receive a dose regarding other characteristics that might influence the risk of developing thyroid disease.

Thus, for the Pilot Study, some of the participants were identified from areas that are geographically removed from the three-county area considered most likely exposed. This design served two important purposes. First, it enabled the evaluation of radiation doses to the thyroid for a group of people anticipated to be relatively unexposed to the atmospheric releases of radioactive iodine from the Hanford Site in a manner identical to that used for people anticipated to be highly exposed. Second, this approach provided information regarding the success rates of the different data collection aspects of the project among people born in areas removed from the Hanford Site relative to people born in areas in close proximity. It was recognized that, to the extent substantial differences in the success of participant enrollment and data collection efforts were identified, revisions in the overall study design would have been necessary.

For a separate geographical area to be suitable as a source of study participants, two conditions must be met: 1) the area must have received little or no exposure to the radioactive iodine from Hanford either directly through atmospheric transport of the iodine or from importation of agricultural products (principally milk) from contaminated areas; and 2) the participants from that area must be as comparable as possible to those from the more exposed area regarding other factors that might influence the risk of thyroid disease. In practice, it may be difficult to define an area that satisfactorily meets the conditions specified by both of these criteria. With increasing distance from the Hanford Site (and, therefore, less likelihood of exposure), there was concern that comparability of other factors would be more difficult to achieve.

Regarding exposure to the atmospheric releases of ^{131}I, initial information available from the HEDR Project about prevailing wind patterns, ^{131}I deposition, and commercial milk distribution suggested that counties to the west and northwest of the Hanford Site might be possible sources of study participants with relatively low doses. Sagebrush concentrations of ^{131}I in the northwestern-most sections of the 10-County HEDR Phase I region were two or three orders of magnitude less than those in areas immediately surrounding the Hanford Site, and these same counties were generally milk surplus areas, meaning that they received little or no milk from cattle in areas likely to be more heavily contaminated by ^{131}I.

Nevertheless, a careful review of the preliminary HEDR Phase I thyroid dose estimates released in July, 1990, indicated that even in these counties some people may have received considerable radiation doses to the thyroid; for example, infants in the eastern Census Divisions of Kittitas County (KI1, KI7, KI8, KI9, KI10, KI11) (see Figure 2.5 in reference (23)). Furthermore, as continuing efforts were made by the HEDR Project to improve the quality and completeness of the basic data regarding meteorology and milk distribution used to calculate radiation doses, it became apparent that appreciable doses possibly occurred in some of the counties outside the 10-County Phase I region (Figure IV.A-1, used with permission, 152).

Thus, based upon the information available at the time about possible thyroid doses, it seemed most prudent to attempt to locate subjects with little or no dose from areas at least one additional county "layer" distant from the Phase I boundary, and more directly to the north of the Hanford Site. Consequently, in the Pilot Study, selection of cohort members was extended to the three counties most directly north of the Hanford Site (Okanogan, Ferry, and Stevens) which are separated from the Phase I 10-county HEDR boundary by one "layer" of counties.

The criterion of comparability of factors other than radiation exposure that might cause thyroid disease was also a concern. Relatively little is well established regarding the causes of thyroid disease. Factors known to be of most potential concern were: 1) selected demographic factors, most notably age, sex, and race; 2) socioeconomic status, most importantly as it relates to access to medical and dental care and resulting exposures to medical and dental sources of ionizing radiation; and 3) dietary iodine intake.

In selecting Okanogan, Ferry, and Stevens counties for inclusion in the Pilot Study, it was important to assess the degree to which the populations of these counties were similar to those of Benton, Franklin, and Walla Walla counties in the 1940s regarding at least the factors listed above. Age and sex

distributions for 13 counties in central and eastern Washington and north-central Oregon that might have been considered sources of people exposed to little or no radioactive iodine from Hanford showed little variability among the counties in the ratio of males to females. Okanogan, Ferry, and Stevens counties were shown to have slightly higher proportions of children under the age of five than do Benton, Franklin, and Walla Walla, but the difference was relatively small.

Figure IV.A-1. Iodine-131 Thyroid Dose from All Exposure Pathways (Milk Cows on Fresh Pasture)

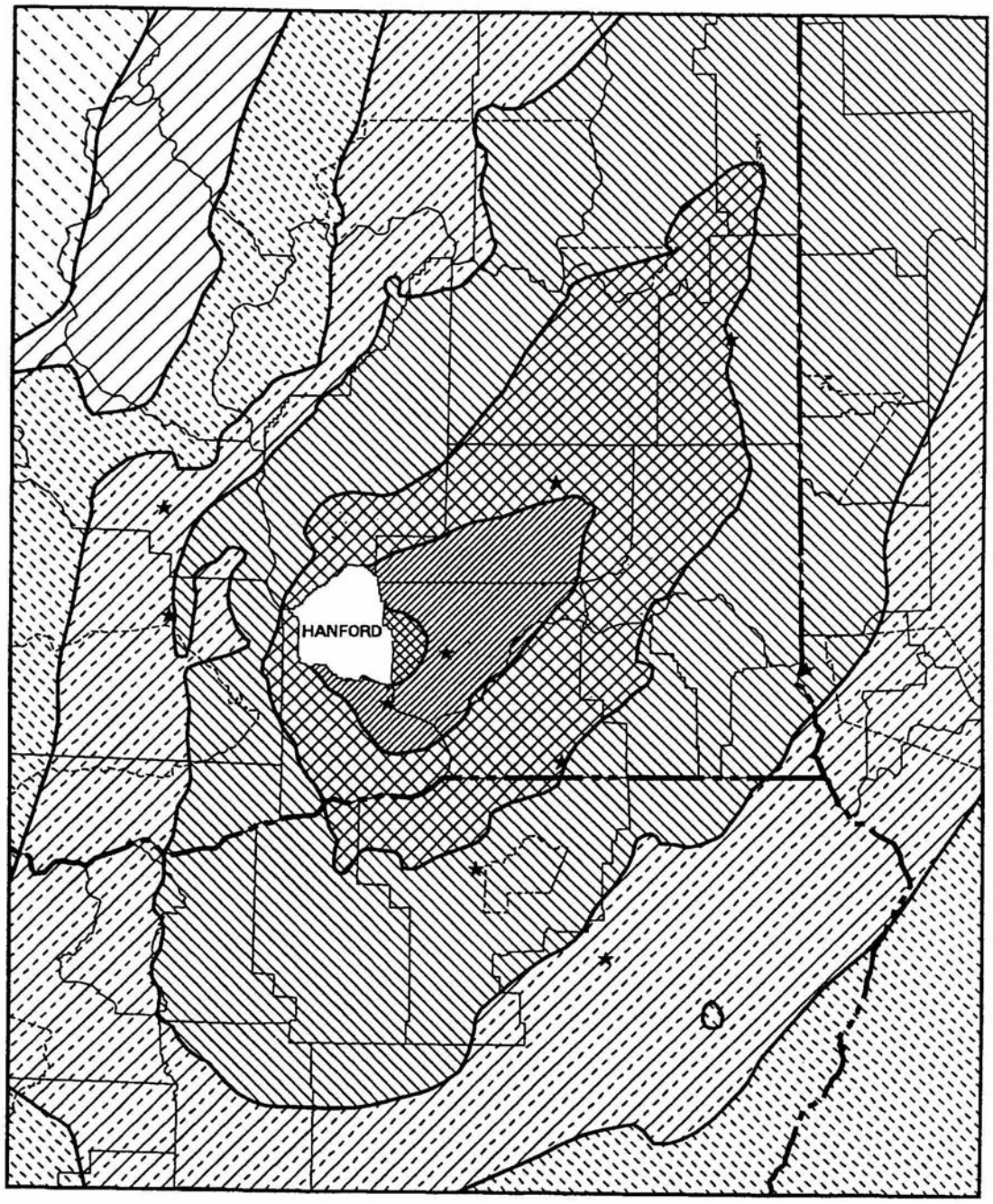
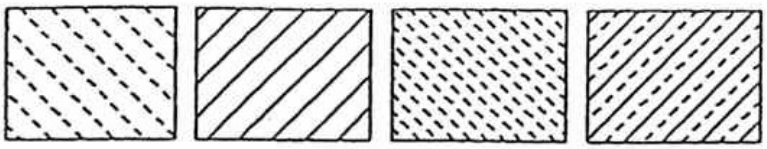
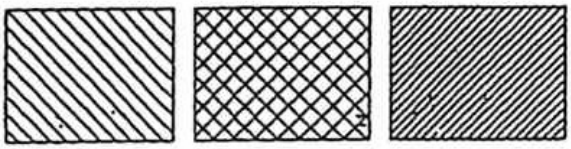


Figure IV.A-1. Legend



Sex/Age Category				
All 0-1 years	0.024 - 0.08	0.08 - 0.24	0.24 - 0.77	0.77 - 2.4
All 1-5 years	0.015 - 0.05	0.05 - 0.15	0.15 - 0.48	0.48 - 1.5
Male 5-10 years	0.010 - 0.03	0.03 - 0.1	0.1 - 0.32	0.32 - 1
Female 5-10 years	0.008 - 0.02	0.02 - 0.08	0.08 - 0.24	0.24 - 0.76
Male 10-15 years	0.006 - 0.02	0.02 - 0.06	0.06 - 0.2	0.2 - 0.61
Female 10-15 years	0.005 - 0.02	0.02 - 0.05	0.05 - 0.17	0.17 - 0.54
Male 15-20 years	0.004 - 0.01	0.01 - 0.04	0.04 - 0.12	0.12 - 0.37
Female 15-20 years	0.003 - 0.01	0.01 - 0.03	0.03 - 0.09	0.09 - 0.29
Male 20-35 years	0.002 - 0.01	0.01 - 0.02	0.02 - 0.07	0.07 - 0.21
Female 20-35 years	0.002 - 0.01	0.01 - 0.02	0.02 - 0.05	0.05 - 0.16
Male >35 years	0.002 - 0.005	0.005 - 0.02	0.02 - 0.05	0.05 - 0.15
Female >35 years	0.001 - 0.004	0.004 - 0.01	0.01 - 0.04	0.04 - 0.13



Sex/Age Category			
All 0-1 years	2.4 - 7.7	7.7 - 24	24 - 65
All 1-5 years	1.5 - 4.8	4.8 - 15	15 - 41
Male 5-10 years	1 - 3.2	3.2 - 10	10 - 27
Female 5-10 years	0.76 - 2.4	2.4 - 7.6	7.6 - 21
Male 10-15 years	0.61 - 2	2 - 6.1	6.1 - 16
Female 10-15 years	0.54 - 1.7	1.7 - 5.4	5.4 - 15
Male 15-20 years	0.37 - 1.2	1.2 - 3.7	3.7 - 10
Female 15-20 years	0.29 - 0.91	0.91 - 2.9	2.9 - 7.7
Male 20-35 years	0.21 - 0.69	0.69 - 2.1	2.1 - 5.8
Female 20-35 years	0.16 - 0.51	0.51 - 1.6	1.6 - 4.3
Male >35 years	0.15 - 0.49	0.49 - 1.5	1.5 - 4.2
Female >35 years	0.13 - 0.42	0.42 - 1.3	1.3 - 3.5

Comparisons of data from the 1940 Census showed that the populations of the counties to be included in the Pilot Study were overwhelmingly classified as rural and white. The median number of years of school completed, and the proportion of the population 14 years of age and older employed in five major occupational groups were also similar. Thus, it was concluded that the composition of the six counties included in the Pilot Study in terms of age, sex, race, education, percent rural, and major occupational category were reasonably similar, and not greatly different from other counties in the larger surrounding region.

It was also important to assess the degree to which iodine availability and/or intake might vary among study counties. Geographical differences in the distribution of iodine intake could result in geographic differences in the rates of one or more of the thyroid diseases under study (e.g., endemic goiter belts). To the extent that such differences might be related to radiation dose from Hanford, they could potentially confound an association between radiation exposure and thyroid disease.

Preferable to estimates of soil iodine concentrations would be estimates of iodine intake. Although little work had been conducted in this regard on a geographic basis, in 1970 Oddie et al. (153) reported estimates of average dietary iodine intake derived from thyroidal radioiodine uptakes in approximately 30,000 euthyroid subjects in 133 locations throughout the United States. Although average daily iodine intake varied considerably throughout the United States (from 240 to 740 micrograms per day), the Pacific Northwest was relatively uniform in the distribution of daily intake estimates. Mean values were reported for fifteen areas in the Northwest centered by two degrees latitude and longitude (approximately 140 by 120 miles). All values in the six Pilot Study counties were between 345 and 379 micrograms per day (a very narrow range compared to the overall distribution of values). Thus, within the confines of most of central and eastern Washington and north central Oregon, there is some evidence to suggest that iodine intake was adequate and relatively uniform in the past.

The inclusion of Okanogan, Ferry, and Stevens counties in the Pilot Study was intended to provide a convenient mechanism for identifying an adequate number of potential study participants who received little or no radiation dose to the thyroid from Hanford. It was not intended to serve as a means of defining a "comparison area" or "control group." Although potential study participants were selected based, approximately, on the county in which they were born (see section V.A., below), the fact that a person was born in one area or another was not relied upon to determine whether he or she was actually exposed to radioactive iodine from Hanford and, more importantly, actually received a radiation dose to the thyroid. Exposure, and the estimate of the resulting radiation dose to the thyroid, was determined from a detailed residential history and exposure information collected whenever possible from the mother or other close relative of each study participant (discussed more fully in section V.D. below). For example, a person born in Benton County between 1942 and 1944 may have moved to a residence away from Hanford before any exposure could occur. Similarly, a person born in Stevens County may have lived or visited for a prolonged time (e.g., a summer) within the "exposed area" and received a substantial thyroid dose.

Nevertheless, it was assumed that most of the study participants with the highest thyroid doses would come from Benton, Franklin, or Walla Walla County, and that most of the participants from Okanogan, Ferry, or Stevens counties would have very low thyroid doses. The use of separate geographic areas was simply a device that would allow a degree of control over participant selection to assure adequate numbers of participants in the Pilot Study who would have thyroid doses at the highest and lowest extremes of the dose distribution.

Based on the results from the HTDS Pilot Study, it was determined that the inclusion of geographically removed populations in the selections for the Transition and Full Study samples was unnecessary. In fact, maximizing the number of participants with the highest doses proved to be of much greater concern. Thus, no additional selections were made from Stevens, Ferry, and Okanogan counties following the Pilot Study selection. In addition, due to the HEDR Project's findings that people in Adams County could be expected to have received higher doses than those in Walla Walla County, the HTDS cohort was completed by selecting people from the Richland, Pasco/Kennewick, Benton County, Franklin

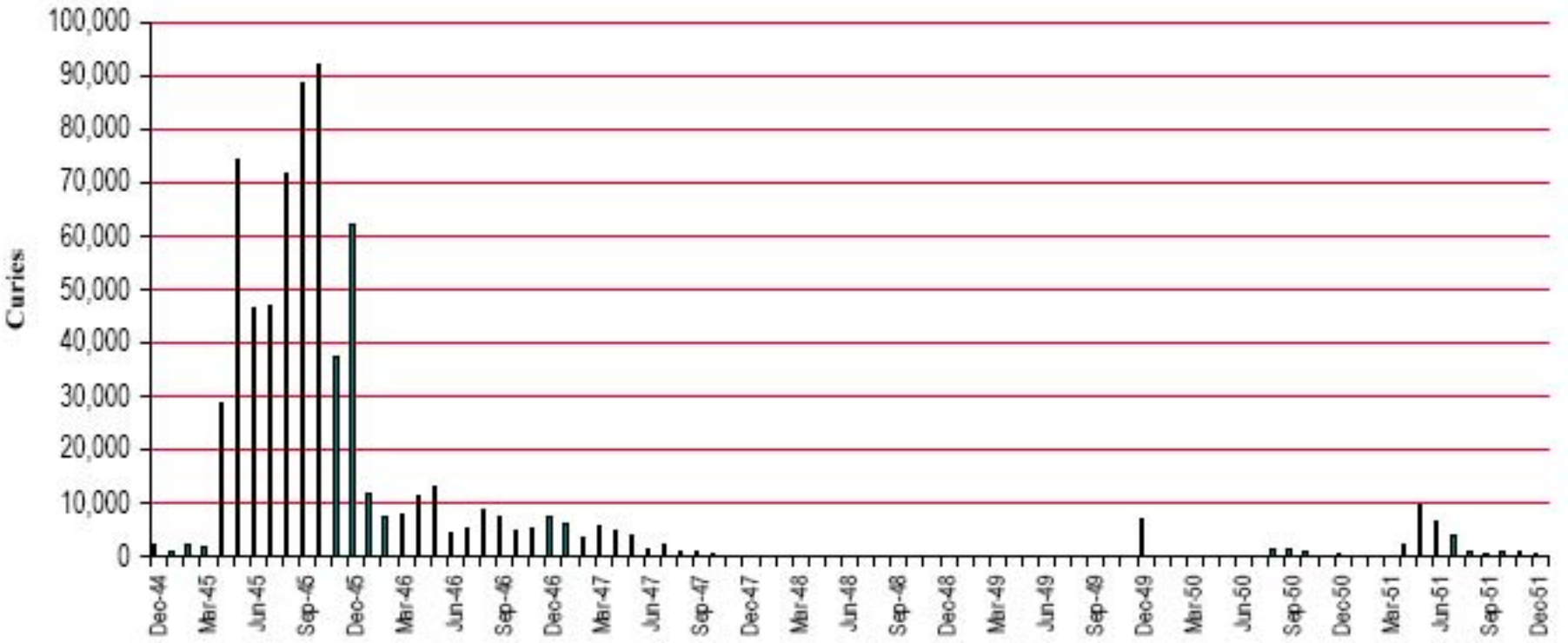
County, and Adams County geostrata.

If it was learned during any part of the study that a potential participant was adopted, the potential participant was considered eligible if verification could be obtained that the birth mother's place of residence at the time of the potential participant's birth was within one of the seven counties included in the study.

A.2. Year of Birth

The radioactivity of ^{131}I decays exponentially with a half-life of 8.4 days. This implies that nearly all of the thyroid dose produced by ^{131}I released into the environment will be accumulated within a few months after its release. Therefore the time period of most interest for identifying potential participants who could have received the highest thyroid doses is that which corresponds to the largest atmospheric releases of radioactive iodine from the Hanford facility. As shown in Figure IV.A-2, the large majority of the releases occurred from the last two weeks of 1944 through 1946. Beginning in 1947, monthly releases were considerably lower, averaging between 100 and 2000 Ci (22). The exceptions to this pattern were the substantial release associated with the "Green Run" in December 1949 and the releases during 1951. Thus, the time during which area residents would likely have received the highest exposure to radioactive iodine would have been the years 1944-1946.

Figure IV.A-2. Monthly ^{131}I Releases from the Hanford Nuclear Site, 1944-1951



Existing literature suggests that age at exposure is an important factor in radiation-induced thyroid disease. In particular, risks among those who are very young at exposure may be higher than for those who are adults at exposure for one or both of the following reasons: 1) higher radiation doses to the thyroid result per unit exposure; or 2) there is an increased sensitivity in the young (i.e., an increased risk per unit dose in the young). It is known that iodine is metabolized differently in children than in adults. The concentration of radioactive iodine in the smaller thyroids of children (the infant thyroid is only about 1/10 the size of an adult thyroid) is greater per unit exposure (45). Book (154) has shown that the thyroid dose to infants resulting from the inhalation of a fixed concentration of radioactive iodine in air is twice that of adults. The dose in near-term infants is ten times that of adults. By the ingestion pathway, six-month-olds could receive thirty times the dose of an adult, largely as the result of smaller thyroids and a higher intake of milk (45).

A number of epidemiological studies have given rise to more indirect evidence regarding the issue of increased sensitivity in the young. Dobyns et al. (55) reported an increased risk of thyroid adenoma among the youngest quartile of a cohort treated with ^{131}I for Graves disease, although risks by specific years of age were not investigated. The incidence of thyroid cancer among atomic bomb survivors in Japan exposed primarily to external gamma radiation has been shown to be higher among those exposed at young ages. A strong dose-response was seen in this cohort, with a three-fold increase in the excess relative risk of children exposed less than 10 years of age compared to those exposed at ages 10-19. Marshall Islanders exposed to nuclear fallout (external gamma and radioactive iodine) had increased rates of thyroid neoplasia at earlier ages of exposure. Compared to people exposed at age 18 and over, those exposed under age 18 had 2.5 times the risk of developing benign nodules and those exposed in utero had a five-fold risk of developing a benign thyroid nodule (69). Results from a study of people treated with radiation for tinea capitis in Israel (external gamma exposure) indicate that children exposed under the age of five had 3.1 times the number of excess thyroid cancers at age 40 than those children exposed over age five (90). Although accurate dosimetry has hampered risk assessment of thyroid cancer from the Chernobyl exposure, it is well documented that a dramatic increase in childhood thyroid cancer has occurred in regions where significant exposure occurred. One recent report showed that since the Chernobyl accident, the incidence of thyroid cancer in 9-year-olds increased 50-fold in the "high exposure area" compared to an increase of 6-fold among 17-year-old children (84). Thus, although none of these results are specific to individual years of age, collectively they indicate a pattern of higher risk for radiation-induced thyroid disease at younger ages relative to adult ages.

Although there are few human studies of exposure to ^{131}I which can adequately evaluate the effect of age at exposure, animal studies have suggested greater carcinogenic risk at younger ages. In ^{131}I uptake experiments in rats, Sikov (155) demonstrated that fetal thyroids were 20 times more sensitive to functional damage than adult thyroids. Corresponding estimates for neonates and weanlings were 3 times and 1.5 times the sensitivity of adult thyroids, respectively. Similar results have been observed in guinea pigs (156). Christov (157) has reported similar findings using external radiation (x-rays) in Wistar rats. Among those irradiated at ten days of age, 40% developed thyroid adenomas whereas only 15% developed these tumors when irradiated at 60 days of age. None of the control rats developed tumors.

Although there are no human data to support age at exposure as an important factor in hyperparathyroidism after ^{131}I exposure, animal studies do provide some evidence that there is an increased frequency of parathyroid tumors in rats exposed to ^{131}I at young ages relative to older ages (98,99).

Based on these data from animal and epidemiological studies, it seems reasonable to expect that the risk of radiation-induced thyroid disease (and possibly hyperparathyroidism) would be greater among those exposed at the youngest ages. Therefore, the Pilot Study was limited to people who were children (ages 0-5) during the periods of greatest atmospheric releases from Hanford (i.e., 1945-1946). Thus, people born from 1942-1946 were eligible for inclusion in the Pilot Study.

This approach was also advantageous regarding important aspects of the fieldwork. Since the primary information to be used in the dosimetry calculations was to be derived from interviews with mothers (or other close relatives or individuals knowledgeable of the participant's childhood), it was important to maximize the probability that such information could be successfully collected and that it would be reasonably accurate. Younger study participants would, in general, have younger parents. Given an average follow-up of about 40 years, the 0-5 year age range at the time of exposure would reasonably assure that most parents of study participants would still be living and able to participate in an interview.

Following the Pilot Study, in order to include greater numbers of participants with thyroid doses in the higher range, it was also necessary to change the years of birth from which potential participants were selected (see section V.A.3 below). Given that the largest exposures would have occurred in 1945, it was thought more advantageous to select births from earlier years, 1940 and 1941, than from years later than those already included in the study. Thus, births from 1940 through 1944 were included in the Full Study selections. While there was some concern that including earlier births would decrease the numbers of participants for whom a CATI respondent could be found, this was not felt to outweigh the need to include as many higher dose participants as possible.

A.3. Other Possible Criteria

It is well established that thyroid neoplasia occurs more frequently in women (45), and there is evidence to suggest an increased risk among the Jewish (45,158). However, no attempt to further restrict eligibility in the Pilot Study based upon sex or ethnicity was made.

Although there are no Reservations in Benton, Franklin, or Walla Walla counties, Native American populations from the region were to be considered in the Pilot Study in an attempt to better define the radiation doses these populations may have received. Most Native Americans did not live in the areas around the Hanford Site where the highest thyroid doses were likely to have occurred. However dietary and/or lifestyle practices specific to one or more of the Tribes and Nations in the region may have been important in contributing to a radiation dose to the thyroid from Hanford's ^{131}I. Thus, as part of the Pilot Study, it was planned to attempt to determine whether the Native American populations in the region experienced exposures to radioactive iodine that could have resulted in significant thyroid doses. Section VII.A. specifies in more detail the conduct of this portion of the study. No attempt was made, however, to exclude people of Native American heritage from participation in the study.

B. Definition of Evaluable Participant

An evaluable participant was defined as one who could be located, who agreed to participate in the study, and for whom sufficient information could be obtained concerning both radiation exposure and thyroid outcomes. For each located participant, every attempt was made to obtain information from all possible sources regarding radiation exposure from Hanford. However, all information of possible use to this study was often not available, especially in view of the length of time that had elapsed since the years of peak exposure. Therefore, for living participants, sufficient information was defined as the following: In-Person Interview and physical examination. Although participants were asked to provide a blood sample and to receive an ultrasound examination (see section V.F, below), those who refused either or both were not deemed non-evaluable. Each participant's final assessment of thyroid or parathyroid disease status was based on the best historical and current information available (as described more fully in sections V.H-V.I).

For deceased subjects, sufficient information was defined as a residence history collected through a surrogate respondent, medical history from a surrogate, and medical record confirmation of thyroid disease reported by a surrogate. It was planned that persons who could serve as surrogate respondents for deceased subjects could include (but were not limited to): a parent, sibling, aunt or uncle of the subject. During the course of the study, it was determined that the plan for conducting CATIs with surrogates for the deceased subjects was not feasible. A discussion of the results of field tests of this portion of the study is contained in section V.D.4 below.

C. Outcome Criteria

This section describes the diagnostic criteria for the thyroid and parathyroid outcomes that are used in this study. Each outcome had two components: 1) the criteria established by the HTDS Study Management Team for the diagnosis of each outcome and 2) an indication of the basis for each diagnosis which serves as a measure of the quality of that diagnosis. The final diagnosis for each outcome included both the presence or absence of the diagnosis and if present, information about the basis of the diagnostic information**.** For example, information about the basis of the diagnosis included whether the diagnosis was made from the HTDS clinic evaluation, obtained from prior medical records with supporting documentation, obtained from prior medical records without supporting documentation, or obtained from a report by the participant or his or her Computer Assisted Telephone Interview (CATI) respondent, without documentation from either the HTDS evaluation or any prior medical records. Diagnostic information obtained from the HTDS evaluation and diagnostic information which was well documented in medical records and met criteria for HTDS diagnoses was considered to be the most definitive and of the highest quality. The primary analysis for each disease outcome was therefore restricted to cases defined according to these two sources. However, additional analyses were performed for each disease outcome using alternative definitions that were more inclusive and less definitive. These alternative definitions are provided in sections IX.C through IX.O below. If a participant had multiple sources of diagnostic information for a particular thyroid disease, with more than one basis for diagnosis, then he or she was classified according to the basis providing the most definitive diagnosis.

C.1. Thyroid Cancer

Diagnostic criteria: Thyroid malignancy according to histopathology reports from a surgical specimen. Original pathology slides were reviewed by the HTDS pathologist, whether the diagnosis was made by HTDS physicians or whether the participant had already had prior thyroid surgery.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of thyroid cancer:

1. Diagnosis originating from HTDS evaluation based on subsequent histology
2. Diagnosis from prior medical record with documentation of histology
3. Clinical diagnosis from HTDS evaluation (no histology available)
4. Clinical diagnosis from prior medical record (no histology available)
5. Participant/respondent report only

C.2. Benign Thyroid Nodule

Diagnostic criteria: Any confirmed documentation of benign histology or cytology as interpreted by a pathologist.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of benign thyroid nodule:

1. Histologic or cytologic diagnosis based on HTDS clinic evaluation
2. Histologic or cytologic diagnosis based on prior medical record documentation
3. Clinical diagnosis from either HTDS evaluation or medical records (clinical impression without cytology)
4. Participant/respondent report only

C.3. Any Thyroid Nodule

Diagnostic criteria: Any thyroid nodule which has been classified as thyroid cancer, a benign thyroid nodule, or a nodule which is suspicious for malignancy or neoplasm. The latter category represents nodules that have cytology suspicious for either malignancy or follicular neoplasm for which no surgery was performed and therefore no histology was available.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of any thyroid nodule:

1. Histologic or cytologic diagnosis based on HTDS clinic evaluation
2. Histologic or cytologic diagnosis based on prior medical record documentation
3. Clinical diagnosis from either HTDS evaluation or medical records (clinical impression without cytology)
4. Participant/respondent report only

C.4. Hypothyroidism

Diagnostic criteria: Elevation of TSH above the upper limit of normal (5.0 μIu/ml) with either low or normal thyroid hormone levels.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of hypothyroidism:

1. HTDS laboratory evaluation
2. Medical records with supporting documentation (elevated TSH)
3. Medical records without supporting documentation
4. Inferred from past or current thyroid hormone therapy
5. Participant/respondent report only

C.5. Autoimmune (Hashimoto's) Thyroiditis

Diagnostic criteria: Positive antithyroid antibody result on either antimicrosomal antibody (AMA) or anti-thyroperoxidase antibody (anti-TPO). Levels above the normal limits for these antibodies (AMA, greater or equal to 25 u/ml; anti-TPO, greater or equal to 2.0 Iu/ml) were considered positive. Participants with positive antibodies but with documentation of Graves disease were not included in this outcome category. Anti-thyroglobulin antibody was also used as an additional antibody marker for an alternative diagnosis of autoimmune thyroiditis (positive result: greater or equal to 1.0 Iu/ml).

Basis for diagnosis. The following categories indicate the basis for the diagnosis of autoimmune thyroiditis:

1. HTDS laboratory evaluation
2. Medical records with supporting documentation (positive anti-thyroid antibodies)
3. Medical records without supporting documentation
4. Participant/respondent report only

C.6. Graves Disease

Diagnostic criteria: Hyperthyroidism present (see # 8 below) with the following additional criteria:
1. Elevated radioiodine uptake and/or thyroid nuclear scan consistent with Graves disease; and/or
2. Exophthalmos

Basis for diagnosis. The following categories indicate the basis for the diagnosis of Graves disease:
1. HTDS laboratory and nuclear medicine evaluation
2. Medical records with supporting documentation
3. Medical records without supporting documentation
4. Participant/respondent report only

C.7. Autoimmune Thyroid Disease

Diagnostic criteria: Defined as having the diagnosis of either autoimmune thyroiditis or Graves disease. See above for diagnostic criteria and basis of diagnostic information for each of these outcomes.

Basis for diagnosis. In general, a diagnosis of autoimmune thyroid disease was simply assigned on the basis for diagnosis of the autoimmune thyroiditis or Graves disease that the participant had. In a small number of instances, participants had diagnoses of both autoimmune thyroiditis based on the HTDS laboratory evaluation or medical records with supporting documentation, and of Graves disease based on medical records without supporting documentation or on participant/respondent report only. In all of these instances, the basis for the diagnosis of autoimmune thyroid disease was taken to be the more definitive, i.e. HTDS laboratory evaluation or medical records with supporting documentation.

C.8. Hyperthyroidism

Diagnostic criteria: Suppressed TSH (less than 0.32 μIu/ml) in the presence of normal or high thyroid hormone levels. The following additional information was collected to further assess the etiology of hyperthyroidism:
1. To evaluate Graves disease or a toxic thyroid nodule as an etiology of a suppressed TSH, repeat thyroid function tests (TSH, T3 and T4 levels), a thyroid nuclear scan and radioiodine uptake were requested (see #6 above).
2. History of current medical treatment with thyroid hormone was obtained to assess exogenous thyroid hormone therapy as a cause of hyperthyroidism. For participants having a suppressed TSH while taking thyroid hormone medication, their hyperthyroidism was presumed to be caused by exogenous thyroid hormone.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of hyperthyroidism:
1. HTDS laboratory evaluation
2. Medical records with supporting documentation
3. Medical records without supporting documentation
4. Participant/respondent report only

C.9. Multinodular Thyroid Gland

Diagnostic criteria: A thyroid gland with abnormal firm consistency with two or more discrete nodules, or multiple firm lobular and/or nodular areas throughout the gland. The definition of thyromegaly in this study is a two-fold enlargement of the thyroid gland based on physical examination. Therefore, the above characteristics of a multinodular gland occurring in a gland enlarged two-fold or more is classified as multinodular goiter whereas these characteristics occurring in a gland of normal size (less than two-fold enlarged) is classified as multinodular gland. The definition of thyromegaly as a two-fold increase in thyroid gland size was chosen as a conservative definition to avoid classifying normal variations as clinical disease. Dominant palpable nodules or those which were nonpalpaple and greater than 1.5 cm in three dimensions underwent FNA biopsy. Such nodules would then be classified as either benign or malignant depending on the results of the biopsy or further thyroid surgery.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of multinodular gland:

1. HTDS physical examination
2. Medical records with documentation of multinodular gland or goiter
3. Participant/respondent report only

C.10. Simple Goiter

Diagnostic criteria: Diffuse thyromegaly (two-fold enlargement) with normal consistency and without palpable nodules or lobulations. The definition of thyromegaly as a two-fold increase in thyroid gland size was chosen as a conservative definition to avoid classifying normal variations as clinical disease. This classification was intended primarily to reflect physiologic thyroid gland enlargement.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of simple goiter:

1. HTDS physical examination
2. Medical records with documentation of diffuse goiter without nodularity or abnormalities in consistency
3. Participant/respondent report only

C.11. Other Thyroid Disease

Diagnostic criteria: This category was designated for any diagnoses of thyroid disease that are not included in the HTDS diagnostic outcomes above. It was primarily a category for participant reports of unknown thyroid disease, diagnosed generally many years ago, and treated with unknown therapy for which no medical records were available.

Basis for diagnosis. The following categories indicate the basis for the diagnosis of other thyroid disease:

1. HTDS evaluation
2. Participant/respondent report only

C.12. Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

Diagnostic criteria: The following categories of ultrasound abnormalities were defined:

1. Palpable ultrasound-detected thyroid abnormalities
2. Nonpalpable focal ultrasound-detected thyroid abnormalities
3. Diffuse (nonpalpable) ultrasound-detected abnormalities of the thyroid
4. Any ultrasound-detected abnormality of the thyroid (any of the above categories)

Basis for diagnosis. All of these definitions were based on only one source of information: HTDS ultrasound examination.

C.13. Hyperparathyroidism

Diagnostic criteria: Defined as hypercalcemia (calcium greater than 10.2 mg/dl) with an elevated PTH level (greater than 65pg/ml).

Basis for diagnosis. The following categories indicate the basis for the diagnosis of hyperparathyroidism:

1. HTDS laboratory evaluation
2. Medical records with supporting documentation
3. Medical records without supporting documentation
4. Participant/respondent report only

V. FIELD PROCEDURES AND METHODS, RESULTS OF DATA COLLECTION PROCESS

A. Cohort Definition, Subject Identification and Selection

A.1. Background

A.1.a. Objectives

The objective of this component of the study was to define and identify a group of people (a cohort) who were exposed to atmospheric releases of radioactive iodine (^{131}I) from the Hanford Nuclear Site between 1944 and 1957. Since the primary objective of the overall study was to determine whether exposure to such radiation resulted in an increased risk of thyroid disease, it was important to identify a cohort within which there would be the greatest likelihood of detecting an association between exposure to ^{131}I from Hanford and thyroid disease, if such a relationship exists. This was to be accomplished by defining a cohort that would contain adequate numbers of people with the highest possible radiation doses to the thyroid from Hanford, as well as people with very low radiation doses to the thyroid from Hanford.

A.1.b. Definition of the Cohort

In seeking to define a cohort that would contain individuals with a full range of exposures to ^{131}I from Hanford, extensive attempts were made to investigate different sources of information that would enable one to construct a comprehensive list of people who might have been exposed. Ideally, such a list would consist of all people in a relatively large population surrounding the Hanford site who were resident during the time period that the largest atmospheric releases occurred, and would contain enough identifying information to ensure that a sufficient number of people could be located nearly five decades after exposure. The following sources of information were investigated in the Hanford region: 1) school enrollment records; 2) school health records; 3) school reunion lists; 4) health department clinic and immunization records; 5) church membership lists; 6) town lists and voter registration records; 7) Census Bureau records; 8) Internal Revenue Service records; 9) property tax and public utility records; and 10) birth records.

Most of these sources of information proved to be inadequate for constructing a sufficiently comprehensive listing of individuals who might have been exposed to Hanford releases. School health records, reunion lists, health department records, church lists, town and voter lists, and property and utility records were all too incomplete. School enrollment records were complete and potentially very useful where they existed, but unfortunately many school districts in the region had destroyed old records and a few denied us access. Census Bureau and IRS records would have been ideal sources for enumerating a population, but access to such information was prohibited by law. Thus, only birth records provided an acceptable source for identifying a cohort.

Birth records provide a complete listing of all people born in a defined geographic area during defined time periods. The records were available at no cost to the study and could be easily accessed by staff. Thus, by abstracting information directly from birth certificates, it was possible to construct a roster of individuals corresponding to specific geographic areas and time periods most relevant to the Hanford releases.

A.2. Plan

A.2.a. Protocol Plan

For the Pilot Study, a birth roster was constructed based on all birth certificates from the counties of Benton, Franklin, Walla Walla, Okanogan, Ferry, and Stevens for the years 1942-1946. As indicated above, complete birth records existed for these counties and were available from the State of Washington Vital Records Division. The following data were abstracted from each birth certificate and entered into a computerized database to form the roster for selection of potential participants: birth certificate number, mother's usual residence, child's name, sex, and birthdate, father's name, mother's name, mother's mailing address, and county of birth.

The field "Mother's Mailing Address" was judged to best indicate the mother's actual residence when the subject was born. However, the birth certificates for births in Benton, Franklin, and Walla Walla counties had been computerized previously for the CDC by the State of Washington, and "Mother's Mailing Address" was not included in this database. Thus only "Mother's Usual Residence" was available and it was felt this might not reflect the mother's actual residence when the subject was born. Therefore, HTDS staff computerized the mailing addresses for those mothers who gave birth in Benton, Franklin, and Walla Walla Counties but whose usual residences were outside the six study counties in order to include those whose "Mother's Mailing Address" lay within the six Pilot Study counties in the roster for subject selection.

For purposes of geographical stratification, "Mother's Residence at the Subject's Birth" was defined for the counties of Benton, Franklin and Walla Walla as follows:

- For births with "Mother's Usual Residence" (birth certificate item 2) in one of the six Pilot Study counties (Benton, Franklin, Walla Walla, Okanogan, Ferry and Stevens), "Mother's Residence at Subject's Birth" was defined as the "Mother's Usual Residence"

- For births with "Mother's Usual Residence" outside the six study counties, "Mother's Residence at the Subject's Birth" was defined to be the "Mother's Mailing Address".

For Okanogan, Ferry and Stevens counties, "Mother's Residence at the Subject's Birth" was defined as the "Mother's Mailing Address."

In addition, birth records for Spokane and Yakima counties were reviewed to ascertain births that occurred in those counties to residents of Benton, Franklin, and Walla Walla counties. "Mother's Residence at the Subject's Birth" for these certificates was also assigned to be the "Mother's Mailing Address." People for whom the "Mother's Residence at the Subject's Birth" was outside the selected counties were excluded from the roster.

Eligibility for the study was limited to people whose "Mother's Residence at the Subject's Birth" was in one of the selected counties.

A.2.a.1. Rationale

As noted in section IV-A above**,** preliminary findings from the HEDR project regarding meteorological conditions affecting the deposition and concentration of radioactive iodine in vegetation, and the patterns of milk production and consumption by county, indicated that people with the highest thyroid doses were most likely to have lived in the area encompassed by Benton, Franklin, and Walla Walla counties. Thus, in the Pilot Study for the purposes of subject selection only, residence at time of birth acted as a surrogate for the anticipated radiation dose to the thyroid from Hanford. Individual thyroid radiation dose could only be estimated from data collected during the study. The selection of cohort members was also extended to include three counties on the Canadian border north of the Hanford site

(Okanogan, Ferry and Stevens). These counties were selected because, based upon the information available at the time regarding possible radiation doses to the thyroid, they could be expected to contribute some cohort members with very low radiation doses to the thyroid from Hanford. In addition, people living in these counties would likely be comparable to those who receive higher thyroid doses in terms of other factors which could potentially influence the risk of thyroid disease (e.g., geography, urban/rural composition, occupational factors, socioeconomic factors, age, ethnicity, sex). Furthermore, similar opportunities and resources existed to identify and trace people in this group as in the group that received a thyroid dose. Thus, a cohort was selected which was expected to contain people whose dose estimates would range from the highest doses received to the lowest.

Preliminary estimates of the HEDR project suggested that the highest thyroid doses were probably in people exposed as infants or children during the first years of Hanford operations. This is because infants and children receive higher thyroid doses per unit exposure due primarily to the small size of their thyroid glands. In addition, existing literature suggests that the risk of radiation-induced thyroid disease (and possibly hyperparathyroidism) is greatest among those exposed at youngest ages (see section II.B. for a more detailed description). For these reasons, the Pilot Study was limited to people born from 1942-46, since the large majority of releases of radioactive iodine from the Hanford facility occurred in 1944-46 (with the exceptions of the "Green Run" in December 1949 and the releases during 1951). Thus, the cohort would contain people whose exposures began as early as the prenatal period, and as late as age three. An additional benefit of choosing this group was that mothers and close relatives of people born during 1942-46 would more likely be alive and available for interview compared to those of people born earlier.

Selection of potential participants from the Birth Roster was stratified by geographical area, year of birth, and sex. The purpose of stratification by geographical area and birth year was to assure that adequate numbers of high dose and low dose participants were identified, and a wide range of doses was obtained. Stratification by sex also reduced the possibility of confounding by sex that could reduce the efficiency of the study.

For purposes of stratified selection of subjects from the Birth Roster, geographical areas were defined to distinguish predominantly rural areas from predominantly urban areas. The reason for such distinction was that it was reasonable to expect that people from predominantly rural areas may have been more likely to consume fresh raw milk than their more urbanized counterparts. If true, and if such consumption patterns were an important determinant of higher dose, it might be important in the Full Study to concentrate potential participant selection from rural areas. At the time of protocol development, HEDR Phase I results indicated that the distinction between fresh raw and commercial milk consumption did not have a substantial effect on the magnitude of estimated thyroid dose (23).

Each person on the Birth Roster was assigned to the area which contained his or her "Mother's Residence at the Subject's Birth," as outlined in section V.A.2.a. Eight geographical areas, called "geostrata" in this report, were defined:

1. Richland
2. Pasco/Kennewick
3. Walla Walla City
4. Benton County outside Richland and Kennewick
5. Franklin County outside Pasco
6. Walla Walla County outside Walla Walla City
7. Okanogan County
8. Ferry and Stevens Counties

A.2.a.2. Completeness Required for Success

For each of the eight geostrata defined above, a target of ten living evaluable participants was sought for the Pilot Study for each sex and year of birth. For geostrata 2-6, there were ten strata (five years of birth x two sexes) for a total target of 100 living evaluable participants in each area. For geostratum 1 (Richland), there were six strata (three years x two sexes, as Richland was not defined as a geostratum prior to 1944) for a total target of 60 living evaluable participants. A target of five living evaluable participants was sought in each of the ten year/sex strata for geostrata 7 and 8 (for a total of 100), however during the Pilot Study sample selection the target of 10 living evaluable participants was actually used, for a total of 200). Thus, the Pilot Study attempted to enroll no less than 560 participants from geostrata 1-6, and 200 participants from geostrata 7-8. As a first approximation, twice this number of subjects was to be selected from the Birth Roster to obtain the overall goal of 760 living evaluable participants. The plan was that if this goal was not achieved (i.e., less than a 50% success rate in locating and enrolling participants), additional subjects would be selected in the same manner.

A.2.b. Plans for Assessing the Need for Change in the Full Study

The feasibility of basing the Full Study on a cohort identified solely from birth certificates depended in part on whether adequate information could be obtained for a sufficiently large proportion of cohort members, and whether the range of thyroid radiation doses obtained was sufficiently wide. However, any decision regarding the roster of subjects for the Full Study (e.g., whether to include additional birth year cohorts or participants identified from other sources, such as school records) would be based on all pertinent information, and not just the data obtained and used to evaluate the above criteria.

It was anticipated that the birth cohort criteria for defining cohort members in the areas most heavily exposed would be expanded for the Full Study. Thus, assuming the same methods for identifying cohort members (i.e., birth certificates), it was expected that additional birth year cohorts might be included. Such an expansion would likely be achieved by including people born before 1942, as this would continue to provide the best opportunity to include people who received relatively high doses during childhood. It would also serve to include a larger range of ages at exposure. However, it might also be possible to expand the range of birth years slightly forward in time as well.

Decisions about whether and how to expand the cohort were to be based largely upon the sample size calculations conducted at the conclusion of the Pilot Study and the resources available to the study. If insufficient numbers of births were available under the current criteria to satisfy the sample size requirements of the Full Study, then clearly it would almost certainly be necessary to expand the cohort to include additional births from other years. If, however, it was not necessary to expand the cohort to meet sample size requirements, such expansion, to the extent that resources allowed, would nevertheless be proposed to increase the generalizability of the results by including a wider population representation in the study. Secondarily, such an expansion would serve to increase the power of the study.

At the time the protocol was written, it was unclear whether the geographical boundaries of the study area would change. It was considered unlikely that the boundaries of the area exposed would be significantly expanded. More likely, it was thought that it might be possible (and advantageous) to restrict the definition of "exposed" areas somewhat, based on the distribution of preliminary doses observed in the Pilot Study.

To determine whether a geographically separate area should be identified, it was planned to evaluate: 1) the dose distributions for participants born in the northern three counties (Okanogan, Ferry, and Stevens); and 2) the degree to which all aspects of data collection among people geographically removed from the Hanford site (and presumed to be less likely to be highly exposed) relative to those in closer proximity was successfully conducted. As described in section III-J.1 of the protocol, collectively, these evaluations would allow a better determination of whether the geographically separate areas chosen

for the Pilot Study would be suitable regarding doses (i.e., that most participants in those geostrata would have relatively low doses) and logistics. It could be, for example, that it would not be necessary to include all of these counties in the Full Study. In contrast, it was also recognized that the results of the Pilot Study could indicate that none of the separate counties would be suitable for use in a Full Study. If such a determination was made based upon dose distributions (and not issues of feasibility of data collection), it would be necessary to explore and define another geographical region or regions more removed from the Hanford Site to maintain the capability of being able to conduct analyses that were not solely dependent on HEDR individual dose estimates. The evaluation of other potential regions would be based primarily on the following factors: 1) meteorological data, 2) milk distribution patterns, and 3) socioeconomic and lifestyle factors.

A.3. Revisions

A.3.a. Rationale for Revisions made in the Transition Sample

Prior to completion of the Pilot Study and before a final determination had been made regarding the conduct of a Full Study, another selection of cohort members was made from the Birth Roster. This was done after consultation with the CDC and the HTDS Federal Advisory Committee, in anticipation of continuing with a Full Study, to maintain continuity in field operations and study personnel. This group, called the Transition Sample, was selected prior to any analyses of the dose data from the Pilot Study. The Transition Sample was selected from each birth year and sex stratum in each of the following geostrata: Richland, Pasco/Kennewick, Walla Walla City, Benton County, and Walla Walla County (further selection from the Franklin County geostratum was not possible since all subjects in that geostratum had already been selected for the Pilot Study sample). The Transition Sample was selected from these geostrata because they were the most likely to have relatively high doses, and it was felt there were already sufficient numbers of low dose participants.

A.3.b. Rationale for Revisions made in the Full Study

The power calculations described in detail in the Pilot Study Report outline the rationale for the revisions made in the Full Study selection (see section V.A-5 below for a brief summary of these calculations). In short, it was determined that the cohort defined for the Pilot Study was likely to be inadequate in size, and that greater numbers of participants in the higher dose range would be needed to ensure sufficient statistical power for the primary dose-response analyses. Therefore, in order to include greater numbers of participants with thyroid doses in the higher range, it was necessary to change the years of birth from which cohort members were selected. Given that the largest exposures would have occurred in 1945, it was thought more advantageous to select births from earlier years, 1940 and 1941, than from years later than those already included in the study. Thus, births from 1940 through 1944 were included in the Full Study selections. While there was some concern that including earlier births would decrease the numbers of participants for whom a CATI respondent could be found, this was not felt to outweigh the need to include as many higher dose participants as possible.

Essentially final results of the HEDR project became available while the HTDS Pilot Study was in progress. These results suggested that the geographical region defining the HTDS cohort should be revised to meet the objective of including as many people with the highest thyroid doses as possible. In particular, the final HEDR results suggested that people born in Adams County might be more likely to have higher thyroid doses from Hanford than those in the Walla Walla geostrata.

The Full Study cohort was therefore defined initially to include the Pilot Study and Transition Samples along with (1) all remaining 1942-44 births in the Richland, Pasco/Kennewick, Benton County and Franklin County geostrata; (2) all 1940-41 births with mother's residence at subject's birth in Benton or Franklin County (which include the Pasco/Kennewick strata); and (3) all 1940-44 births with mother's

residence at subject's birth in Adams County. These birth years and geostrata were selected to ensure the inclusion of more high dose participants, based on the dose estimates for hypothetical representative individuals in the HEDR final report of April 21, 1994.

The definition of the cohort was expanded one time, after it was determined that the number of birth certificates obtained was lower than had been projected. Originally it had been projected that 3427 living evaluable participants would be found in the Full Study cohort. However, after obtaining the birth certificates, because there were fewer births than anticipated and the Pilot Study showed there would be fewer living evaluable participants than originally estimated, this projection was reduced to 3006. Therefore, the cohort was expanded to include all remaining births between 12/31/44 and 6/30/45 in the Richland, Pasco/Kennewick, Benton, and Adams County geostrata (no births in the Franklin County geostratum remained unselected). This increased the projected number of living evaluable participants from 3006 to 3277, thereby maintaining essentially the same levels of power as originally projected.

A.4. Outcome and Final Results

The final definition of the cohort was as follows:

1. All births from 01/01/40 to 06/30/45 (in the study counties searched for occurrence births) with mother's residence at subject's birth in Benton, Franklin, or Adams counties (including the Richland and Pasco/Kennewick geostrata).
2. A randomly selected subset of births from 07/01/45 to 12/31/46 in the same counties with mother's residence at subject's birth in Benton or Franklin counties (including the Richland and Pasco/Kennewick geostrata).
3. A randomly selected subset of births from 01/01/42 to 12/31/46 with mother's residence at subject's birth in Walla Walla County (including the Walla Walla geostratum) or Okanogan, Ferry, or Stevens counties.

Table V.A-1, below, shows the birth years within each geostratum from which subjects were selected, by each phase of selection. Three separate selections were conducted to complete the Full Study Sample, after the Pilot Study and Transition Samples were selected. Table V.A-2 shows the numbers of participants selected in each of the 100 strata for the Full Study. Note that all people in the 1940-1944 birth cohorts for Benton, Franklin and Adams Counties (including the Richland and Pasco/Kennewick geostrata) were selected.

Table V.A-1. Birth Years Included in Each Phase of Participant Selection

	Phase of Selection				
Geographic Area	Pilot	Transition	Full 1	Full 2	Full 3
Richland	1944-46*	1944-46	1944		1/45-6/45
Pasco/Kennewick	1942-46	1942-46	1942-44	1940-41	1/45-6/45
Walla Walla City	1942-46	1942-46			
Benton County	1942-46*	1942-46	1942-44	1940-41	1/45-6/45
Franklin County	1942-46			1940-41	1/45-6/45
Walla Walla County	1942-46	1942-46			
Okanogan County	1942-46				
Ferry/Stevens Counties	1942-46				
Adams County				1940-44	1/45-6/45

* The city of Richland was defined as a geostratum separate from Benton County beginning in 1944.

Table V.A-2 Distribution of Birth Year, Sex, and Geostratum for the Full Study Cohort

		Birth Year														
		1940		1941		1942		1943		1944		1945		1946		
Geostratum		F	M	F	M	F	M	F	M	F	M	F	M	F	M	Total
Richland*	Births									92	93	234	230	237	197	1083
	Selected									92	93	142	128	43	44	542
	% Selected									100	100	60.7	55.7	18.1	22.3	50.0
Pasco/	Births	63	77	84	82	84	83	140	162	216	228	209	209	243	204	2084
Kennewick	Selected	63	77	84	82	84	83	140	162	216	228	131	127	41	40	1558
	% Selected	100	100	100	100	100	100	100	100	100	100	62.7	60.8	16.9	19.6	74.8
Walla Walla	Births					179	205	184	182	260	255	300	336	307	322	2530
(city)	Selected					44	41	41	40	40	42	40	42	41	41	412
	% Selected					24.6	20.0	22.3	22.0	15.4	16.5	13.3	12.5	13.4	12.7	16.3
Benton	Births	75	47	69	71	52	71	85	86	176	187	60	67	72	75	1193
County*	Selected	75	47	69	71	52	71	85	86	176	187	51	57	48	50	1125
	% Selected	100	100	100	100	100	100	100	100	100	100	85.0	85.1	66.7	66.7	94.3
Franklin	Births	19	19	7	20	22	17	12	13	23	20	11	14	15	22	234
County	Selected	19	19	7	20	22	17	12	13	23	20	11	14	15	22	234
	% Selected	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Walla Walla	Births					47	53	46	66	66	71	71	58	84	80	642
County	Selected					47	53	46	44	44	48	48	54	42	40	466
	% Selected					100	100	100	66.7	66.7	67.6	67.6	93.1	50.0	50.0	72.6
Okanogan	Births					217	236	255	280	222	237	227	253	317	306	2550
County	Selected					21	22	21	20	21	22	21	21	21	21	211
	% Selected					9.7	9.3	8.2	7.1	9.5	9.3	9.3	8.3	6.6	6.9	8.3
Ferry/	Births					231	233	215	234	178	197	125	117	198	227	1955
Stevens	Selected					21	21	22	21	22	22	21	24	22	20	216
Counties	% Selected					9.1	9.0	10.2	9.0	12.4	11.2	16.8	20.5	11.1	8.8	11.0
Adams**	Births	30	31	37	36	37	44	45	44	48	45	17	21			435
County	Selected	30	31	37	36	37	44	45	44	48	45	17	21			435
	% Selected	100	100	100	100	100	100	100	100	100	100	100	100			100
Total	Births	187	174	197	209	869	942	982	1067	1281	1333	1254	1305	1473	1433	12706
	Selected	187	174	197	209	328	352	412	430	682	707	482	488	273	278	5199

* The city of Richland was defined as a geostratum separate from Benton County beginning in 1944.
** 1945 Adams County number of births is for January-June only (all other geostrata include some July-December 1945 births).

A.5. Summary of Full Study Power Calculations, as Presented in HTDS Pilot Study Report

Two primary objectives of the Pilot Study were to assess the suitability of areas chosen for the selection of study participants, and to utilize Pilot Study dose information and response rates to estimate sample sizes required to achieve adequate statistical power for a Full Study. As is often the case with observational studies such as the HTDS, sample size and dose distribution cannot be chosen independently. In particular, as the sample size increases, the relatively small groups of subjects likely to have the highest doses are all selected, and further selections must be made from the relatively larger groups of people likely to have smaller doses. As a result, beyond a certain number, the effect of increasing sample size is to a certain extent offset by the effect of decreasing mean and variance of the resulting dose distribution.

As described in Appendix H of the HTDS Protocol (1), the primary power calculations focused on tests of the dose-response for the endpoint of thyroid neoplasia (malignant and benign). Calculations were also performed for two additional endpoints: thyroid malignancy and ultrasound-detected abnormality of the thyroid (thyroid UDA). These three outcomes were selected since they provided a range of baseline outcome percentages: low (malignancy), intermediate (thyroid neoplasia), and high (UDA). Sample sizes were calculated for the χ^2 test for linear trend in the cumulative incidence of disease with stratification by sex. In particular the sample size N required for the one-sided test with critical level α to achieve statistical power $1-\beta$ to detect a dose-response coefficient B is given by the formula:

$$N = \left(z_{1-\alpha} - z_{\beta}\right)^2 \Bigg/ \left[1 \left(z_{1-\alpha} - z_{\beta}\right)^2 \Bigg/ \left[B^2 \sigma^2 \sum_{i=1}^{I} \frac{\pi_i}{P_i^*\left(1 - P_i^*\right)} \right] \right]$$

where
$z_p = \Phi^{-1}(p)$ denotes the 100p-th percentile of the standard normal distribution,
$i = 1,2$ indexes the $I=2$ sexes,
π_i = proportion of the N participants of sex denoted by i,
σ^2 = variance of the dose distribution, and
$P_i = P_i(\mu) = A_i + B\mu$ is the probability of disease for sex denoted by i and dose equal to the mean dose μ.

This formula indicates that, as is typically the case, the required sample size is largely determined by the variance σ^2: in particular the required sample size is roughly inversely proportional to σ^2. The effect of the mean dose is much more limited. For a given sample size N, the equation above can be solved for the power $1-\beta$. This approach was used under various assumptions about sample size, and power was displayed in figures as a function of the dose-response coefficient B. The resulting plot indicates in a comprehensive way the power of the planned analyses to detect radiation effects of various magnitudes.

The approach taken in the analysis of the Pilot Study results was to project the mean and variance of doses that might be obtained under various plans for selecting subjects to complete the sample for a Full Study. Consideration focused on three such plans:

Plan 1:

Remaining sampling would be restricted to birth records from 1942-44 for the Richland, Pasco/Kennewick, Benton County, and Franklin County regions. All remaining subjects from these strata would be included in the Full Study.

Plan 2:

In addition to Plan 1, the definition of eligibility would be expanded to include births during 1940-41 to mothers whose residence at time of birth was in Benton and Franklin Counties, and all such births would be included in the Full Study. Note that these two counties include Pasco and Kennewick, which do not need to be distinguished as a separate geographical region.

Plan 3:

In addition to Plan 2, the definition of eligibility would be expanded to include births during 1940-44 to mothers with residence at the time of birth in Adams County, and all such births would be included in the Full Study.

Note that Plan 1 required only projections based on dose data available from the Pilot Study, while Plans 2 and 3 required projections of dose distributions for years and/or regions not included in the Pilot Study. The methods for calculating projected means and variances for both types of projections were described in Appendix B of the Pilot Study Final Report.

The projected sample sizes, means and variances for these three plans, based on all dose data available from either the Pilot Study sample or the combined Pilot Study and transition sample, are shown in Table V.A-3.

Table V.A-3. Sample Size (N) and Projected Dose Mean and Variance (rad) of Full Study Dose Distribution for the Three Additional Sampling Plans

		Pilot Only (n=869)		Pilot and Transition (n=1139)	
Plan	N	Mean	Variance	Mean	Variance
1	2619	13.7	361.1	14.5	372.9
2	3081	13.5	353.6	14.4	367.3
3	3427	14.6	393.8	15.4	404.3

The HTDS was based on a cohort of people defined by the following eligibility criteria:

- Mother's residence at the time of the participant's birth: Benton, Franklin, Walla Walla, Okanogan, Ferry, Stevens, or Adams County in Washington State
- Year of birth: 1940 – 1946.

The rationale for this choice of counties and years is described in sections IV.A.1 and IV.A.2 below. The mother's usual residence at the time of the participant's birth, which can be determined from birth records, was used as a criterion since it was likely to indicate the participant's place of residence during the first years of Hanford's operations, when the largest releases of ^{131}I occurred (see section V.A.2 below). The cohort included the majority of the possible combinations of the seven counties and seven birth years. However birth year subcohorts for certain counties were not included since they were unlikely to include many participants with relatively high thyroid radiation doses (see sections V.A.2 and V.A.3 below).

Power functions of tests for dose-response based on the projections derived from the Pilot Study only are shown in Figures V.A-1 through V.A-3 for the endpoints of thyroid neoplasia (benign and malignant combined), thyroid cancer, and thyroid UDAs. In each figure, the lowest curve is based on Plan 1, and the highest on Plan 3.

Figure V.A-1. Projected Power Function: Thyroid Neoplasia Plans 1, 2 and 3

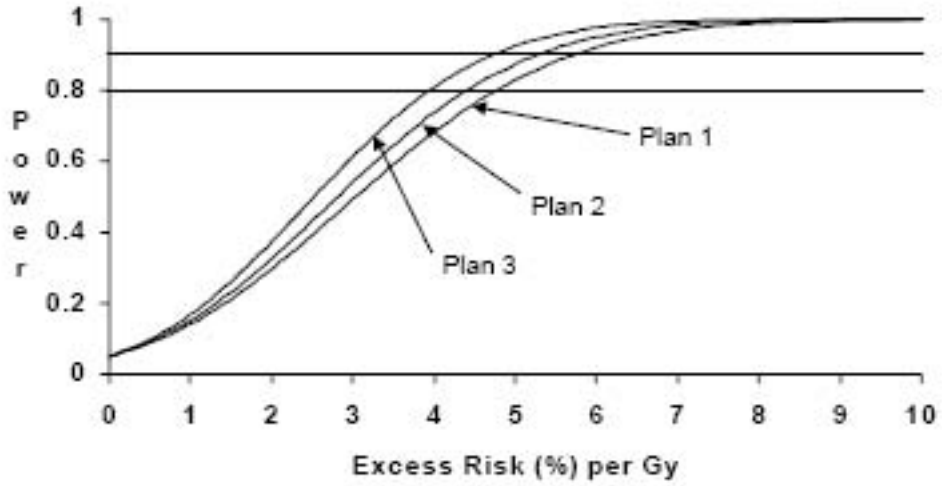


Figure V.A-2. Projected Power Function: Thyroid Malignancy Plans 1, 2, and 3

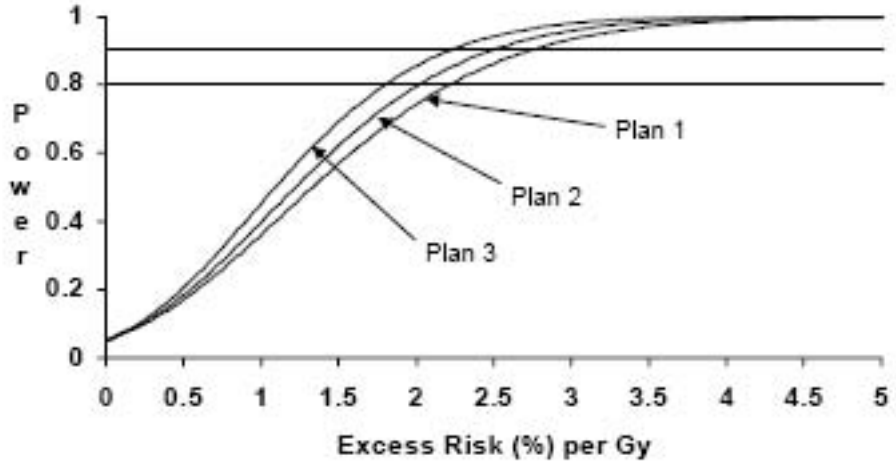
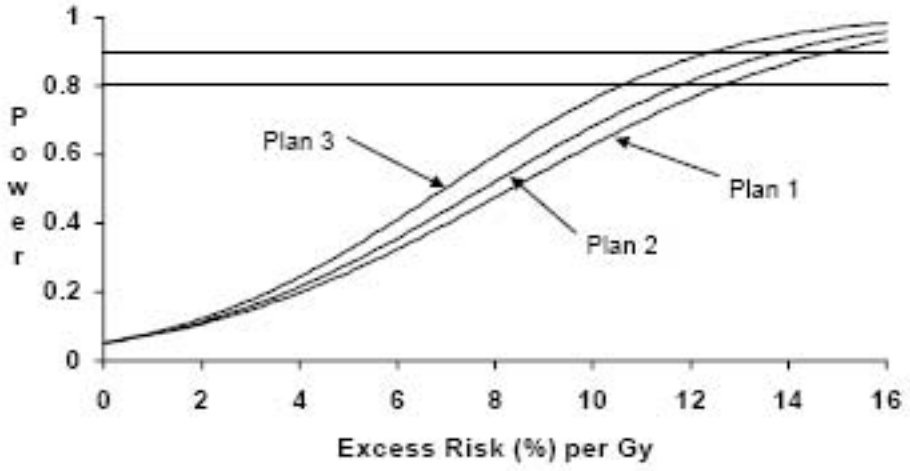


Figure V.A-3. Projected Power Function: Ultrasound Detected Abnormalities of the Thyroid Plans 1, 2 and 3



For the analysis of thyroid neoplasia (defined in the Protocol and Pilot Study as "all thyroid nodules)," the baseline percentages of patients with disease were taken as 5% for women and 2% for men (see Appendix H of the HTDS protocol for the derivation of these percentages). Based on data from the 869 Pilot Study participants, Plan 1 was projected to provide power of 0.83 to detect a dose-response coefficient of 5% per Gy. Under Plans 2 and 3 this increased to 0.87 and 0.92, respectively (Figure V.A-1). Thus with Plan 3 there would be adequate power to detect about a doubling (tripling) of risk among women (men) at 1 Gy (1000 mGy). This magnitude of effect is similar to that projected from the relative risk model of BEIR V as described in Appendix H of the HTDS protocol. It is also comparable to that recently reported for the Utah Study. Kerber et al. (53) reported a significant radiation dose-response for thyroid neoplasia during 1965-86 (p=0.019), with an estimated relative risk of 8.0 at 1 Gy (95% lower confidence bound 1.7).

The baseline percentages of participants with thyroid malignancy were taken to be 0.7% for women and 0.3% for men (see Appendix H of the protocol). Plans 1, 2, and 3 were projected to provide power of 0.80, 0.90, and 0.94, respectively, to detect a dose-response of 2.5% per Gy (Figure V.A-2).

For an analysis of thyroid UDAs, the baseline percentage of participants with such findings was taken as 40% for both sexes, based on information available from reports of thyroid ultrasound screening in unselected populations and the experience in the Pilot Study. Plans 1, 2, and 3 were projected to provide power of 0.90, 0.94, and 0.97 to detect a dose-response of 15% per Gy (Figure V.A-3).

A number of assumptions were made in the projections of statistical power described above. To assess the sensitivity of the projections to these assumptions, i.e., to assess whether deviations from any of these assumptions might lead to significant changes in the projected levels of power, additional power calculations were performed with these assumptions modified. The following assumptions were examined in these sensitivity calculations: 1) baseline rates of disease, 2) projected sample size, 3) doses from expanded In-Person Interviews, 4) doses for participants born during 1940-41, and 5) Adams County doses. In addition, the combined effects of deviations in more than one of these assumptions were investigated. The detailed results of these sensitivity calculations were provided in the Pilot Study Final Report (pages 55-74). Based on the results, the following conclusions were reached:

1. Cohorts identified from birth records were likely to provide a sufficiently wide distribution of doses for successful completion of a Full Study.

2. The cohorts defined for the Pilot Study were likely to be inadequate for completing a Full Study, and they should be augmented by the additions of 1940-41 Benton and Franklin Counties and 1940-44 Adams County births.

As described above, the modification proposed in the second conclusion was adopted. However, following the collection of the birth certificate data for the additional birth years and Adams County, and the analysis of more complete data regarding participation rates, it was apparent that further expansion of the cohort was needed. This was accomplished by extending the range of birth dates for Benton, Franklin, and Adams Counties to June 30, 1945.

B. Tracing Potential Participants

B.1. Background

The HTDS was conducted as a follow-up cohort study. Members of the study cohort were identified based on location of birth in the early to mid-1940's from birth certificates. Consequently, extensive effort would be required to locate cohort members, who were young children at the time of exposure, as adults nearly fifty years later. In addition, to identify all past and present thyroid disease in cohort members, participation in the study could not be limited to telephone contact, but would require in-person attendance for medical evaluation regardless of the participant's current area of residence.

B.1.a. Objectives of Tracing

The primary objective of the tracing was to identify a current address and telephone number for all living potential participants, so they could be recruited to participate in the study. A second objective was to obtain confirmation of death, as well as date and cause of death for all those deceased.

B.1.b. History of Tracing Efforts Around Hanford

Prior to the HTDS, a separately funded study had been conducted by investigators at the FHCRC to determine if former residents of the Hanford area could be traced to their current residences for the purposes of an epidemiologic study of radiation releases from the Hanford site. The primary objectives of this preliminary study were: 1) to design and test field procedures for identifying a group of potentially exposed persons; 2) to attempt to trace each person forward in time to the present or until death; 3) to obtain a current address and/or telephone number for each person; 4) to explore the feasibility of interviewing people identified; and 5) to explore the feasibility of obtaining medical records to verify self-reported illness histories.

The population selected for this preliminary study was defined by the rural area directly east of the Hanford Nuclear Site in Franklin County, containing 37 farm blocks subdivided into approximately 1897 farm units. Four farm blocks were randomly selected from the area, two being in the area of the two research interviewers' homes, and two being remote from these areas. In this manner, it was hoped that each interviewer would be working within an area that was very familiar and within which she would personally know the residents, as well as in one area which was quite unfamiliar.

Each interviewer was to obtain as much information as possible about anyone who resided in the assigned farm blocks from the time they were first inhabited until the present. Most farm blocks were first inhabited in the early 1950's due to the Columbia Basin Land Reclamation Project. However, some farm blocks were inhabited as early as 1909.

The principle sources of information the interviewers used to initially identify the population living in the selected farm blocks was a title company in Pasco, Washington which recorded a complete record of ownership for each farm unit. Because ownership records do not include family members or other residents, additional information was obtained through library references, telephone books, personal visits, and telephone calls. Thus, a chronology of persons who resided in each farm unit was constructed.

A total of 126 persons were found to have resided on the 14 occupied farm units within the four farm blocks. This number includes primary owners/residents, their children, employed farm workers and their families. For all but four residents (3%), actual years of residency were ascertained. Sixty-four (51%) residents lived on the farm units for some period between 1949 and 1965, a time period that encompassed much of the radioactive releases from Hanford.

Of the 126 persons identified, ten (8%) were documented to be deceased. An additional eight persons (6%) could not be located. Slightly more than half of those identified and located were currently still living on the farm units. Another 15% were resident in the immediate area, and 5% were within Washington or a neighboring state. The remainder of those located resided in the Western U.S.

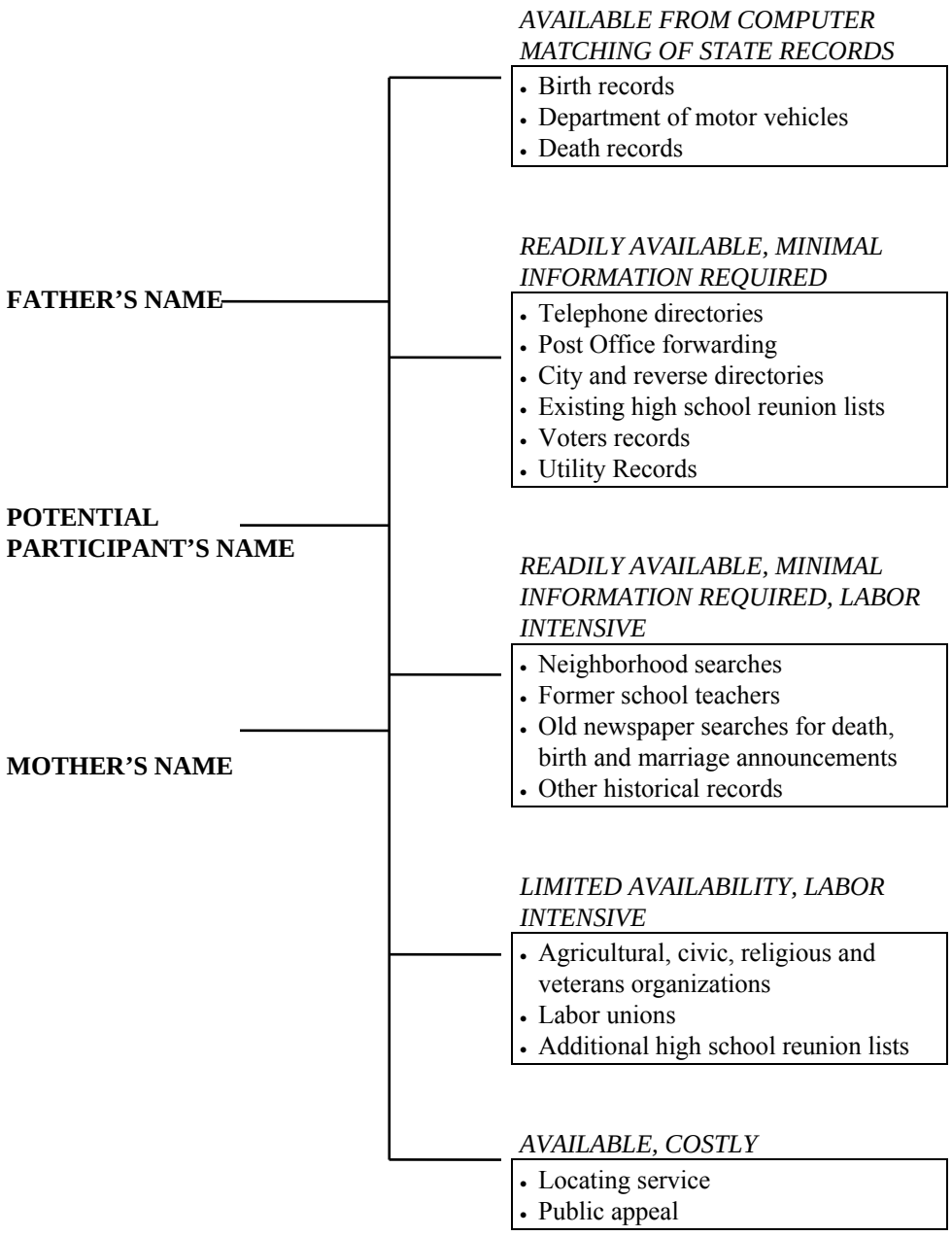
The results suggested that identifying, tracing, and locating residents of this region during the time period of interest regarding Hanford radiation releases was feasible, at least for the more rural segment of the population.

B.1.c. Overview of Tracing Efforts

At the time the HTDS protocol was written, tracing and locating large numbers of people who were born in the areas of interest up to 50 years ago presented significant logistical challenges. It was presumed this would be particularly true for women, many of whose surnames would have changed at least once in the intervening years because of marriage.

The initial approach to locating and tracing individuals is depicted graphically in Figure V.B-1. As shown in the diagram, searches were initiated based on the cohort member's name, the father's name and the mother's name. At the start of the search, efforts were concentrated on locating any one of these three individuals until enough information was obtained to focus on the location of the potential participant. The tracing process was to be undertaken as an investigative process, using different sources, as they needed to be pursued. The sources depicted were generally pursued in the order shown, beginning with the most readily available, least costly and least labor intensive, and progressing toward the most costly and most labor intensive until the potential participant was located or until all reasonable effort had been expended. See below for a more detailed description of the tracing effort.

Figure V.B-1. Locating and Tracing Potential Participants



Initially, two approaches were utilized to trace potential participants. The first was a series of computer matches of the study cohort to databases maintained by the State of Washington. These included: 1) death certificates; 2) recent birth certificates (second generation births), linking through both the father's and mother's name (i.e., the potential participant's name); and 3) Department of Licensing (Driver's License and Motor Vehicle Registration) information. The second approach was to use readily available and relatively inexpensive sources. These included primarily searches of telephone books, city directories, and Cole's reverse directories. In addition, several school reunion lists had already been obtained, and additional lists were sought as sources of potential participant follow-up. Field staff also searched for information using the Social Security Death Index kept by the Genealogical Library of the Church of Jesus Christ of Latter Day Saints**.** This source was particularly useful in locating family members through the deceased parent's Social Security payments.

Persons not located with the computer matches or through the use of readily available sources were sought using more intensive search methods including the use of county records of marriage records, and using local libraries to search old newspapers for obituaries, wedding and birth announcements. An attempt to locate individuals not found using any of the above sources was made through contacts in the communities.

To minimize the potential for bias in locating cohort members that might be related to either exposure or disease status, it was decided that several possible sources of information would not be used. These included population-based tumor registries, unsolicited self-report by members of the public, and mailing lists related to Hanford issues. Because each of these sources could be the only means of locating some persons, and inclusion in these sources might be related both to exposure status and/or thyroid disease status, they were specifically avoided for tracing purposes.

When contacting people who may have had information on the potential participant's location, such as the potential participant's mother or father, they were told that we were attempting to locate people who had been selected from birth certificates to participate in a medical research study. If the contact requested additional information, they were told that the study was the Hanford Thyroid Disease Study and were given basic information about the study. If the person requested additional information before disclosing the location of the potential participant, he or she was advised to contact the Seattle office toll-free telephone line. When contacting potential study participants a script was used to provide basic information about the HTDS and to inform them that a letter would be sent explaining the study in detail. If more information about the study was needed, the potential participant was advised to call the Seattle office toll-free telephone number and speak with the Participation Coordinator**.**

B.1.d. Staffing and Logistics

The tracing field staff consisted of several employees located in eastern Washington. A procedure manual was used to prioritize steps to be taken in locating potential participants. Records of each step in the search for each potential participant were kept to learn more about the most efficient methods for locating potential participants. Regular meetings were held in the Tri-Cities with the Project Manager and Principal Investigator to assess the success of this component throughout the fieldwork phase of the study.

B.2. Revisions to the Original Protocol Plan

B.2.a. Deletion of Ineffective Sources of Information and Addition of New Sources

During the Pilot Study, it was determined that some of the more difficult to use and often most expensive sources were less effective and these were not actively pursued in the Full Study. For example, high school reunion lists were moderately helpful in the Pilot Study (useful information was obtained in 41% of the cases in which such lists were used), but required rather extensive efforts to obtain. Overall, school records were not a major source of tracing information. The use of a locator service toward the end of the Pilot Study proved to be very expensive per potential participant located, and the results varied considerably. This source

was not routinely used beyond the Pilot Study, but was replaced by sources mentioned below, provided by the newly developed FHCRC Tracking Resource Center (TRC).

The use of more intensive contacts in small communities in the region was explored in the last few months of the Pilot Study Tracing process. Study staff made several trips during the Pilot Study to small towns to talk to local citizens and "old-timers" and to look through local records (e.g., marriage, utilities, property records). In general, these trips were moderately successful but labor intensive. Local postmasters, teachers, and community leaders were able to provide some guidance, and often helped to gain access to local records that might otherwise have been difficult to obtain. Such sources were used for only a very few potential participants, but when it was appropriate to pursue such sources, they were generally very successful in locating that potential participant.

In summary, the experience gained in the Pilot Study tracing effort identified a number of key approaches and sources of information that proved to be useful in locating potential participants. These approaches and sources defined the primary methodology used in locating the remaining potential participants needed for a Full Study. Those methods and sources that did not prove to be as useful were reserved for the most difficult to locate, when other resources had been exhausted.

B.2.b. Addition of Computer On-line Database Information

Late in the tracing process for the Full Study, a Tracking Resource Center (TRC) was developed by the FHCRC. This resource was designed to provide tracing, locating, and tracking services to a number of Center projects needing to identify and locate study participants or former patients. The TRC was utilized by the HTDS to locate potential participants who could not be located by other means. Additional new resources available through the TRC were: 1) a national, on-line database resource providing matches by name and previous address; and 2) a national, on-line database providing matches by name and date-of-birth, linking multiple public records available at that time. While the use of these resources tended to be more expensive, they were less labor intensive and frequently provided leads to assist in locating individuals who were the most difficult to locate.

B.3. Final Tracing Process

Tracing of potential participants was conducted in three stages, in the following chronological order for most potential participants. The first stage consisted of a series of linkages with publicly available data sources. The second stage, which constituted the majority of the tracing effort, utilized a variety of resources to look for potential participants on an individual basis. The third stage, undertaken only for those individuals most difficult to locate, was to enlist the services of the newly created FHCRC Tracking Resource Center and/or a professional locating company.

B.3.a. Linkages with Publicly Available Data Sources

Five types of linkages to publicly available data sources were performed on either the entire study sample or the appropriate subgroup, based on type of linkage. First, the study sample was manually matched to Washington State infant death certificates for the years 1942-1950 for the six original Pilot Study Counties

(not including Adams).[1] Second, the study sample was matched by computer to the Washington State Death Index (WSDI) for the years 1965-1990.[2] This included some records for Washington State residents who died outside of Washington, which were obtained through interstate exchange agreements. For females, matching to the death index was based on the potential participant's birth name from the birth certificate and the Father's surname as reported on the death certificate. Third, the Pilot Study sample was manually matched to a list of Washington State Vietnam War deaths. Because of the low return from searching the Vietnam War Deaths list (only one match was found for the entire Pilot Study sample), routine searching of this list was not continued for all potential participants in the Full Study samples, but was referred to as appropriate for more difficult to locate individuals.

The fourth step was perhaps the most unusual linkage undertaken in this series of linkages. Washington State birth certificates list mother's maiden (or birth) and current name, father's name, mother's and father's ages, and the child's name. To use this information to find study participants, female potential participant birth names were matched to mother's maiden name on Washington State birth certificates for the period 1956-1990 (second generation births), primarily to identify possible married names. For matches found in this way, the child's last name was assigned as a potential married name for the mother.

Fifth, the names of the entire study sample (including possible married names obtained in step four, above) were matched to the Washington State Department of Licensing (WSDOL) Driver's License Records by name and date of birth. This match was periodically re-run during the course of the study as the WSDOL records were updated. Matches were also conducted individually as new possible married names, children's names, and spouse names were identified.

After the final linkages for the entire group were performed and some potential participants located, three additional linkages were performed only on potential participants not yet located. For the Pilot Study, potential participant parents' names were matched by computer to the WSDI (1965-1990), using father's name, mother's maiden name and mother's potential married name from the potential participant's birth certificate. The purpose of this link was to provide dates and place of death for parents for whom an obituary could then be found. Because most obituaries list the survivors (including current names and place of residence), this information was sometimes used to locate the potential participant or a relative of the potential participant. Since the parents' dates of birth were not available on birth certificates (only age was listed), this linkage resulted in many possible matches and was not repeated for the Full Study Sample.

The second additional linkage performed for potential participants not located initially was to match males to father's name on Washington State birth certificates from 1956-1990 (second generation births) to identify possible children, through whom the potential participant may be located. Children identified this way were then matched to the WSDOL records.

The final computer linkage, completed only for the Pilot Study, was to match female potential participants' names (both birth and potential married names) to centralized Washington State marriage records, stored on microfiche, from 1970-present. New potential married names identified through this linkage were then matched to the WSDOL records. For the Full Study, this search was done on an individual basis, mainly at the county level, as the same access to these files was not possible at the time of the Full Study.

During the Full Study, matching against the National Death Index (NDI) files became available. The NDI is a central computerized index of death record information since 1979, compiled by the National Center of Health Statistics from information submitted by state vital statistics offices. Each record contains a standard set of identifying data for each decedent. Matches were performed for all potential participants not already located. In addition, parent names from the potential participant's birth certificate were matched for some potential participants. In this way, the informant listed on the parental death certificate could be used as a source for locating the potential participant.

[1] Infant death certificates were not routinely reviewed for 1940 and 1941 due to access problems.
[2] The WSDI was reviewed for all subjects classified as unable to locate throughout the tracing process, the most current issue of the WSDI was periodically reviewed for individuals not located in initial attempts.

Several scenarios were possible for information on a given potential participant from the data linkages. These included:

1. Data linkage shows potential participant deceased: For all potential participants linked to a Washington State Death Record, a death certificate (DC) was requested from the state. While these linkages were performed as "exact matches" (highest possible likelihood that this is the right person), great care was taken to check the death certificate against the birth certificate for any indication that this may be a mismatch.

2. Data linkage shows potential participant linked to subsequent birth: For female potential participants linked to subsequent births, the data from the match were checked against all information entered on the potential participant birth certificate and tracing sheet. If this appeared to be a likely match and a potential married name was elicited, tracing efforts were then directed toward this name until such time that it was confirmed this was indeed the right person.

3. Data linkage shows new address based on WSDOL: Linkage to this source was performed using birth certificate names as well as possible new names generated from the subsequent births listing. The new address information represented the current address held by the WSDOL for that person. The date the information was given to WSDOL as valid was included in the listing.

B.3.b. Manual Tracing Resources

Following the data linkages performed on the potential participant roster database, information was transferred to the eastern Washington staff to conduct tracing efforts manually for each individual. A copy of each potential participant's birth certificate was included in a file created for each potential participant which also included the tracing forms specifically designed for use in this study for documentation of tracing efforts undertaken (See Appendix 3).

The second stage of tracing activity utilized numerous sources identified and pursued by HTDS study staff. In general, after the initial linkages were complete and the matches provided, the tracing staff first undertook the process of locating those potential participants with the most promising information available. This approach was taken to ensure a steady supply of potential participants to be recruited and scheduled for clinics and to keep the study progressing as efficiently as possible. For example, potential participants (or their parents) with exact matches to the WSDOL data (providing addresses) were next searched through telephone directories, city/reverse directories and/or CD-ROM directories and other available resources.

Following the Pilot Study, several changes were made to the databases used to record tracing information. Information on the usefulness of sources was no longer collected. In addition, some sources, such as newspapers, were split into two or more categories to better capture the purpose of their use, such as locating obituary information. For this reason, separate tables are shown here for the Pilot Study Sample, and Transition and Full Study Samples. Tables V.B-1 and V.B-2 display the number of potential participants for whom each manual source was ever used for those in the Pilot Study Sample, and those in the Transition and Full Study Samples.

Overwhelmingly, the primary sources of information for tracing potential participants were telephone directories, family members, and various public records. Initially, phone book searches were conducted by hand, utilizing current and historical phone books obtained by the study and those available in local and regional libraries. Consequently, nearly all (97%) cohort members selected during the Pilot Study were sought in phone books (Table V.B-1). Early in the Pilot Study, however, CD-ROM products listing published phone numbers throughout the United States were acquired for this purpose and used extensively, but did not replace telephone directory use. About half of cohort members in the Transition and Full Study samples were sought in phone books, and 89% on CD-Rom directories (Table V.B-2). Directory assistance throughout the United States was also used extensively. Of the other types of sources used, the Social Security death rosters, City and County records (e.g., marriage records), and obituary information from newspapers and funeral homes were used the most. The category "Other Sources" in the following tables includes numerous other approaches

utilized by tracing staff that were limited to a very few potential participants for any given source. Table V.B-3 depicts the usefulness of sources in locating potential participants, based on the Pilot Study experience.

Table V.B-1. Tracing Sources Used, All Potential Participants – Pilot Study Sample

Source*	Source Was Ever Used (N=1587) †	
	No. of Potential Participants	Percent of Potential Participants (%)
Directories		
• Telephone directories (hard copy)	1546	97.4
• CD-ROM telephone directories	769	48.5
• Directory assistance	691	43.5
• City/Reverse directories	542	34.2
• CA People Finder/Western Gold	8	0.5
School Records		
• High school reunion lists	187	11.8
• Other school records	13	0.8
• Alumni organizations	8	0.5
• School registration records	4	0.3
• Former school teachers	2	0.1
Other Specific Sources		
• Relatives	850	53.6
• Social Security roster	689	43.4
• City/county records (includes marriage records)	307	19.3
• Locating service	189	11.9
• Online services*	130	8.2
• Death certificates	80	5.0
• Newspapers	63	4.0
• Funeral home/cemetery	56	3.5
• Neighborhood searches	51	3.2
• HTDS-ID letters	36	2.3
• Employers	35	2.2
• Libraries	28	1.8
• Postal service	17	1.1
• Veterans organizations	14	0.9
• Letter to Social Security Administration	12	0.8
• Native American sources (tribes and IHS)	9	0.6
• Other HTDS participants	9	0.6
• Birth certificates	8	0.5
• Religious organizations	6	0.4
• Civic organizations	6	0.4
• Agricultural organizations	4	0.3
• Utility records	2	0.1
• Labor unions	2	0.1
• Voter registration	2	0.1
• Military reunion lists	1	0.1
• Historical documents	1	0.1
Other sources	56	3.5

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
† Excludes 3 potential participants for whom no tracing data were entered due to a clerical error.

Table V.B-2. Tracing Sources Used, All Potential Participants – Transition and Full Study Samples

Source*	Source Was Ever Used (N=3475)†	
	No. of Potential Participants	Percent of Potential Participants (%)
Directories		
• CD-ROM telephone directories	3106	89.4
• Telephone directories (hard copy)	1750	50.4
• Directory assistance	1014	29.2
• City/reverse directories	919	26.4
• CA People Finder/Western Gold	28	0.8
School records		
• High school reunion lists	121	3.5
• School registration records	9	0.3
• Former school teachers	1	< 0.1
Other specific sources		
• Relatives	1440	41.4
• Social Security roster	1410	40.6
• Obituaries/funeral homes	1070	30.8
• Death index/death records	565	16.3
• Online services	491	14.1
• Marriage licenses	289	8.3
• Response to HTDS-ID letter	166	4.8
• Tax assessors	76	2.2
• Neighborhood searches	45	1.3
• Postal service	33	0.9
• Employers	32	0.9
• Locating service	22	0.6
• Letter to Social Security Administration	16	0.5
• List of Vietnam veterans	10	0.3
• Military locator service	10	0.3
• Voter registration	9	0.3
• Labor unions	3	0.1
• Other city/county records	3	0.1
• Civic organizations	2	0.1
• Agricultural organizations	2	0.1
• Religious organizations	2	0.1
• Veterans organizations	1	< 0.1
• Utility records	1	< 0.1
Other sources	90	2.6

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
† Table excludes n=134 potential participants who were not entered into the HTDS tracing system. All but one of these potential participants (n=133) were located with information obtained from record linkages with the Washington state Department of Licensing, prior to the implementation of the revised tracing system for transition and full study potential participants. As a result of clerical error, the remaining potential participant was never entered into the tracing system and, therefore, was not traced.

Table V.B-3. Usefulness of Tracing Sources in Locating Study Potential Participants – Pilot Study Only (N=1587)†

Source*	Source was Ever Used** No.	%	Source Lead to or Resulted in Locating Potential Participant No.	% ††
Directories				
• Telephone directories (hard copy)	1543	97.2	1165	75.5
• CD-ROM telephone directories	762	48.0	744	97.6
• Directory assistance	664	41.8	523	78.8
• City/reverse directories	535	33.7	240	44.9
School records				
• High school reunion lists	184	11.6	75	40.8
• Other school records	13	0.8	12	92.3
• Alumni organizations	8	0.5	7	87.5
• School registration records	4	0.3	2	50.0
• Former school teachers	2	0.1	0	--
Other specific sources				
• Relatives	820	51.7	812	99.0
• Social Security roster	672	42.3	312	46.4
• City/county records (includes marriage records)	304	19.2	154	50.7
• Locating service	187	11.8	85	45.5
• Newspapers	63	4.0	56	88.9
• Death certificates	51	3.2	44	86.3
• Neighborhood searches	50	3.2	32	64.0
• Funeral home/cemetery	35	2.2	28	80.0
• Employers	33	2.1	28	84.8
• Libraries	28	1.8	27	96.4
• Postal service	16	1.0	14	87.5
• Veterans organizations	14	0.9	7	50.0
• HTDS-ID letters	13	0.8	13	100.0
• Letter to Social Security Administration	12	0.8	12	100.0
• Native American sources (tribes and IHS)	9	0.6	7	77.8
• Other HTDS participants	9	0.6	9	100.0
• Birth certificates	8	0.5	8	100.0
• Religious organizations	6	0.4	6	100.0
• Civic organizations	6	0.4	5	83.3
• Agricultural organizations	4	0.3	4	100.0
• Utility records	2	0.1	1	50.0
• Labor unions	2	0.1	0	--
• Voter registration	1	0.1	1	100.0
• Military reunion lists	1	0.1	1	100.0
• Historical documents	1	0.1	1	100.0
Other sources	56	3.5	49	87.5

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
** These numbers differ from those in Table V.B-2 as this table contains only tracing performed prior to the end of the Pilot Study, after which information on usefulness of sources was no longer collected.
† Excludes 3 potential participants for whom no tracing data were entered due to a clerical error
†† Percent of those for who source was ever used.

B.3.c. Unlocated Potential Participants

Extensive efforts were made to locate each potential participant identified through birth certificates. While the tracing effort was extremely successful, not all potential participants could be located from the minimal information provided by a birth certificate from 50 years ago. Tables V.B-4 and V.B-5 show efforts expended on potential participants not located. Before efforts were closed out on any individual potential participant, an extensive amount of effort was required. This effort included all of the linkages performed in the initial tracing phase, along with four primary sources that would be tried for everyone. These sources included telephone directories, CD-ROM telephone directories, the Social Security death roster or WSDI, and one on-line service as mentioned above. These represented the only manual sources that were appropriate to try for all potential participants.

Table V.B-4. Tracing Efforts for Those Not Located – Pilot Study Sample

Source	Source Was Ever Used (N=78) No.	Percent of Unlocated (%)
Directories		
• Telephone directories (hard copy)	77	98.7
• CD-ROM telephone directories	77	98.7
• City/reverse directories	62	79.5
• Directory assistance	61	78.2
• CA People Finder/Western Gold**	5	6.4
School records		
• High school reunion lists	11	14.1
• School registration records	2	2.6
• Other school records	1	1.3
• Alumni organizations	1	1.3
Other specific sources		
• Social security roster	75	96.2
• Online services**	70	89.7
• Locating service	48	61.5
• City/county records (includes marriage records)	45	57.7
• Death certificates	21	26.9
• Relatives	11	14.1
• Neighborhood searches	5	6.4
• Funeral home/cemetery	5	6.4
• HTDS-ID letters	5	6.4
• Letter to Social Security Administration	4	5.1
• Newspapers	3	3.8
• Libraries	2	2.6
• Postal service	2	2.6
• Employers	1	1.3
• Native American sources (tribes and IHS)	1	1.3
• Other HTDS participants	1	1.3
• Birth certificates	1	1.3
• Agricultural organizations	1	1.3
• Labor unions	1	1.3
• Voter registration	1	1.3
Other sources	3	3.8

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
** Sources initiated during the transition/full study

Table V.B-5. Tracing Efforts for Those Not Located – Transition and Full Study Samples

Source	Source Was Ever Used (N=242) No.	Percent of Unlocated (%)
Directories		
• CD-ROM telephone directories	240	99.2
• Telephone directories (hard copy)	218	90.1
• City/reverse directories	155	64.0
• Directory assistance	122	50.4
• CA People Finder/Western Gold	26	10.7
School records		
• High school reunion lists	20	8.3
• School registration records	2	0.8
Other specific sources		
• Social security roster	232	95.9
• Online services	225	93.0
• Obituaries/funeral homes	158	65.3
• Death index/death records	139	57.4
• Marriage licenses	48	19.8
• Relatives	25	10.3
• Response to HTDS-ID letter	20	8.3
• Tax assessors	11	4.5
• Postal service	6	2.5
• Neighborhood searches	5	2.1
• List of Vietnam veterans	4	1.7
• Locating service	3	1.2
• Letter to Social Security Administration	3	1.2
• Military locator service	3	1.2
• Employers	2	0.8
• Voter registration	2	0.8
• Civic organizations	2	0.8
Other sources	13	5.4

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.

Tracing potential participants based on birth certificates from the 1940s required the use of multiple sources of information in most cases. After the initial linkages were performed, more than one source of information was used for virtually all of the potential participants being traced. This is because even when a computer linkage was made (e.g., with WSDOL files), at least one additional step was almost always required to obtain information sufficiently detailed to contact the potential participant (e.g., a telephone number). For those most difficult to locate, many sources may have been used before the potential participant was located or determined to be unlocatable. Tables V.B-6 and V.B-7 summarize the extent to which multiple sources were used in the Pilot Study Phase and the Transition and Full Study Phases, by tracing outcome. The number of sources used after the initial linkages ranged from 1 - 16, with a mean of 4.8 sources per potential participant for the Transition and Full Study Phases.

Table V.B-6. Number of Sources Used to Trace Located and Unlocated Individuals – Pilot Study Sample

Number of Sources Used	Located		Unlocated		Total	
	No.	%	No.	%	No.	%
1	13	0.9	0	--	13	0.8
2	264	17.5	0	--	264	16.6
3	242	16.0	0	--	242	15.2
4	214	14.2	1	1.3	215	13.5
5	206	13.7	3	3.8	209	13.2
6	188	12.5	8	10.3	196	12.4
7	135	8.9	16	20.5	151	9.5
8	111	7.4	13	16.7	124	7.8
9	50	3.3	13	16.7	63	4.0
10	37	2.5	10	12.8	47	3.0
11	28	1.9	6	7.7	34	2.1
12	9	0.6	5	6.4	14	0.9
13	4	0.3	2	2.6	6	0.4
14	3	0.2	1	1.3	4	0.3
15	3	0.2	0	--	3	0.2
16	0	--	0	--	0	--
17	2	0.1	0	--	2	0.1
Total	1509	100.0	78	00.0	1587†	100.0
Mean no. of sources	4.99		8.54		5.16	

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
† Table excludes 3 potential participants for whom no tracing data were entered due to a clerical error.

Table V.B-7. Number of Sources Used to Trace Located and Unlocated Individuals – Transition and Full Study Samples

	Located		Unlocated		Total	
No. of Sources Used	No.	%	No.	%	No.	%
1	108	3.3	0	--	108	3.1
2	474	14.7	2	0.8	476	13.7
3	664	20.5	1	0.4	665	19.1
4	563	17.4	0	--	563	16.2
5	334	10.3	11	4.5	345	9.9
6	307	9.5	19	7.9	326	9.4
7	240	7.4	38	15.7	278	8.0
8	210	6.5	46	19.0	256	7.4
9	149	4.6	48	19.8	197	5.7
10	93	2.9	30	12.4	123	3.5
11	50	1.5	23	9.5	73	2.1
12	22	0.7	12	5.0	34	1.0
13	9	0.3	5	2.1	14	0.4
14	7	0.2	5	2.1	12	0.3
15	2	0.1	2	0.8	4	0.1
16	1	< 0.1	0	--	1	< 0.1
Total	3233	100.0	242	100.0	3475†	100.0
Mean no. of sources	4.80		8.69		5.07	

* The sources listed in this table do not include record linkages performed prior to entry of potential participants into the tracing system.
† Table excludes n=134 potential participants who were not entered into the HTDS tracing system. All but one of these potential participants (n=133) were located with information obtained from record linkages with the Washington state Department of Licensing, prior to the implementation of the revised tracing system for transition and full study potential participants. As a result of clerical error, the remaining potential participant was never entered into the tracing system and, therefore, was not traced.

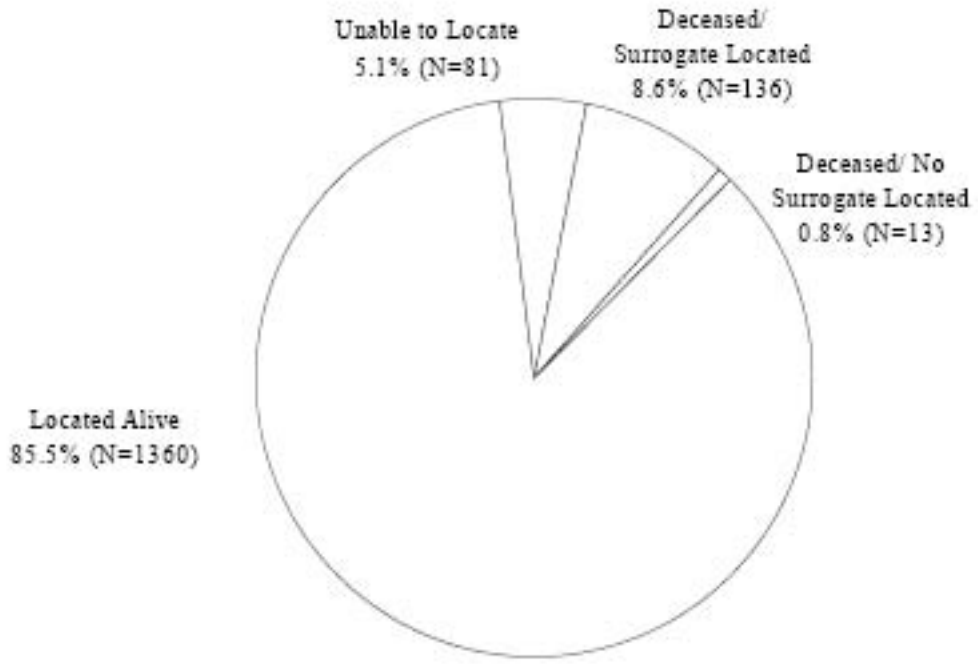
The effort expended toward the location of each potential participant was reviewed by the Data Collection Specialist (DCS) responsible for the case and by the Lead Data Collection Specialist or the Participation Supervisor to assure that all reasonable effort had been made and that all appropriate resources had been used to locate the individual. Only after this review was any potential participant "retired" as unable to locate. At least five sources were used for 316 of the 320 unlocated participants, and an average of more than eight sources were used before potential participants were "retired."

B.4. Outcome and Final Results

B.4.a. Results from the Pilot Study Sample

Figure V.B-2 displays the results of the tracing of individuals selected for the Pilot Study Sample. It should be noted that these numbers vary slightly from the Pilot Study Report of January 24, 1995, as additional potential participants from the Pilot Study selection were included in the Full Study. Of the 1590 individuals selected for the Pilot Study Sample, 1360 living individuals were located and 149 individuals were confirmed deceased. For 136 of the deceased individuals, a surrogate (ie. someone who might be able to provide study information about the deceased individual) was located. Thus, 94.9% of the original sample were located. Only 81 (5.1%) potential participants were listed as "unable to locate."

Figure V.B-2. Tracing Outcome for Pilot Study Sample (N = 1590)



B.4.a.1. Results by Strata

Figure V.B-3 presents tracing outcomes separately for the 791 females and the 799 males in the Pilot Study Sample. Success in locating living individuals was approximately the same for both sexes (87.2% for females and 83.9% for males). However, a larger proportion of Pilot Study Sample males were confirmed deceased (11.8%) than females (7.0%). Thus, after combining the living potential participants with the confirmed deceased, 95.6% of the Pilot Study Sample males and 94.2% of the females were located. This finding was somewhat unexpected, as it was anticipated that females would be much more difficult to locate after such a long period of time, due to name changes with marriage, particularly among this age group.

Figure V.B-3. Tracing Outcome for HTDS Pilot Study Sample, by Sex (N = 1590)

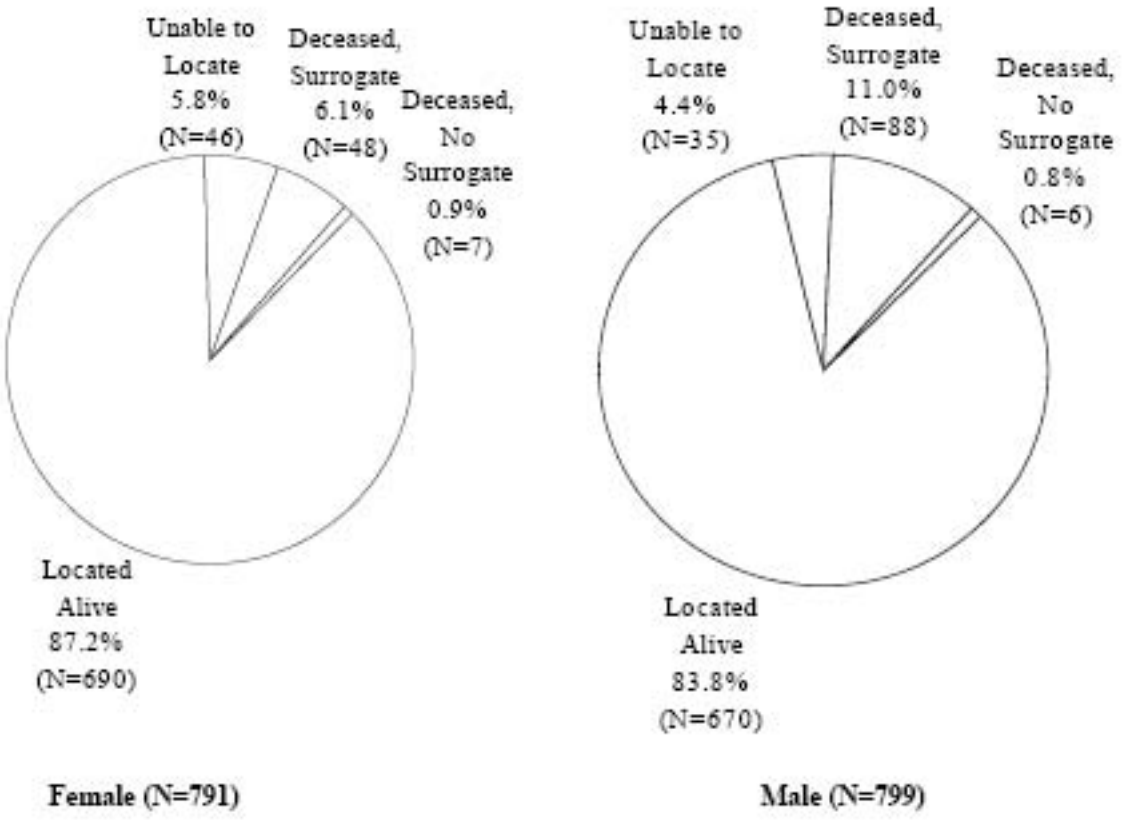


Figure V.B-4 displays the percent of the Pilot Study Sample located according to year of birth, from 1942-1946. There was relatively little difference in the proportion located in each birth year (range = 92.8% to 97.4%). Persons born in 1942 were slightly more frequently located than those born in the other years, but not substantially so.

Figure V.B-4. Tracing Outcome for Pilot Study Sample, by Year of Birth (N = 1590)

Figure V.B-5 displays the percent of the Pilot Study Sample located according to the eight regions that defined the geographic sampling strata (geostrata). These are arranged in the figure to correspond in an approximate manner to more urbanized areas (Richland, Pasco/Kennewick, and Walla Walla city) and predominately rural areas (counties, outside city). Although there is relatively little difference in the proportion located across the eight regions, there was a tendency for the more rural areas to have higher success rates. Such a pattern might be expected given that it is likely that the temporary workers who came to the area for construction jobs at the Hanford facility lived in more urban areas. In four of the five rural geostrata, 95% or more of the potential participants were located. Location rates for the three urban geostrata areas ranged from 89.3% to 93.6%.

Figure V.B-5. Tracing Outcome for Pilot Study Sample, by Geostratum (N = 1590)

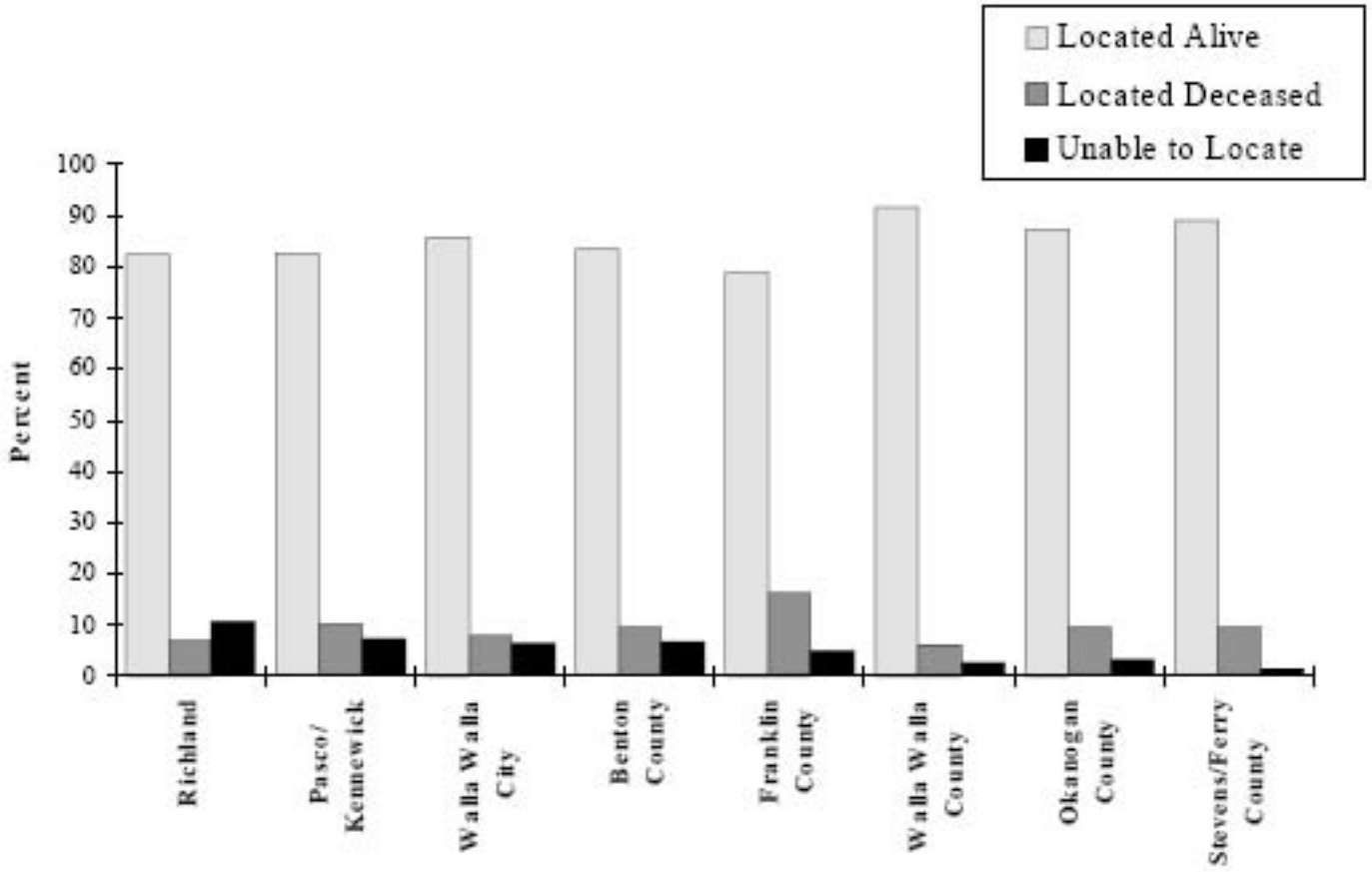


Table V.B-8 shows the proportion of Pilot Study Sample members located within each of the 76 strata (defined by gender, year of birth, and geostrata). More than half the sample was located in all 76 strata. At least 90% of the potential participants were located in 69 (90.8%) of the strata and at least 80% were located in 75 (98.7%) of the strata. In one stratum, 1944 Richland females, only 18 of 23 (78.3%) were located.

Table V.B-8. Percentage of Pilot Study Potential Participants Located in Each of the 76 Sampling Strata -Pilot Study Sample (N= 1590)

Geostratum and Sex**	Year of Birth 1942 No.	1942 %	1943 No.	1943 %	1944 No.	1944 %	1945 No.	1945 %	1946 No.	1946 %
Richland										
Female	See*		See*		18	78	19	90	18	86
Male	Footnote*		Footnote*		21	91	21	100	20	91
Pasco/Kennewick										
Female	21	100	18	90	21	95	16	80	18	90
Male	20	95	19	90	18	90	22	100	19	95
Walla Walla (city)										
Female	22	100	18	90	18	90	17	85	19	95
Male	19	95	20	100	19	90	20	95	20	95
Benton County										
Female	26	100	19	90	18	82	17	85	24	100
Male	22	92	19	90	20	95	22	100	24	96
Franklin County										
Female	21	95	12	100	22	96	7	88	16	100
Male	16	94	13	100	17	94	9	90	19	90
Walla Walla County										
Female	24	100	23	100	22	100	24	100	19	90
Male	26	96	22	100	23	96	26	96	19	95
Okanogan County										
Female	20	95	21	100	20	95	19	90	21	100
Male	22	100	19	95	21	95	20	95	21	100
Ferry/Stevens Counties										
Female	21	100	22	100	22	100	21	100	21	95
Male	21	100	20	95	21	95	24	100	20	100

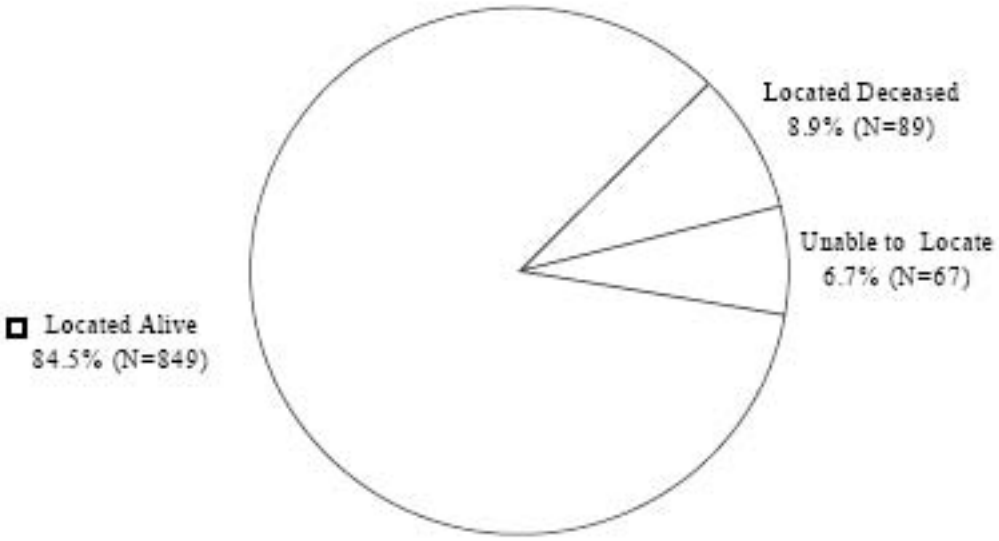
* Richland was defined as a geostratum separate from Benton County only for births in 1944-1946.
** Sex is defined as actual sex, not sex strata, as 2 potential participants were misclassified: one potential participant in the 1945 Pasco/Kennewick stratum was misclasssified as female and another potential participant in the 1946 Franklin County stratum was misclassified as male.

In summary, the Pilot Study demonstrated the feasibility of locating cohort members identified from birth certificate records from the early to mid-1940s. Overall, 91% of the 1590 Pilot Study Sample members identified from birth certificates were located by the end of the Pilot Study in December 1995. By the end of the Full Study, this percentage rose to 94.9%. Success in locating people did not differ substantially according to sex, year of birth, or geographic area of birth. This indicated that the methods used throughout the Pilot Study were effective at locating a substantial percentage of all selected potential participants.

B.4.b. Results from Transition Sample

The Transition Sample selection included potential participants from five of the eight geostrata used during the Pilot Study (Richland, Pasco/Kennewick, Walla Walla City, Benton County outside of Pasco, Walla Walla County outside of Walla Walla City). No further selections were made from the Okanogan or Ferry/Stevens geostrata because it was anticipated that the design of the Full Study would limit further selections to only geostrata near Hanford. No further selection from the Franklin County geostratum was possible, since all its members were selected for the Pilot Study. Figure V.B-6 shows the tracing outcomes for potential participants in the Transition Sample. A slightly lower percentage of potential participants were located in the Transition Sample (93.3%) than the Pilot Study Sample (94.9%). (Note that the category, "Deceased, Surrogate Located" was used only in the Pilot Study, as it was initially intended that deceased potential participants would be represented in the study by a surrogate, when available. Please see section V.D for a complete discussion of this issue.)

Figure V.B-6. Tracing Outcome for the Transition Sample (N = 1005)



B.4.b.1. Results by Strata

Figure V.B-7 shows tracing outcomes by sex for the Transition Sample. Tracing efforts were slightly more successful in locating males than females. This difference was more evident in the Transition Sample (95.0% vs. 91.6% of males and females respectively) than in the Pilot Study Sample (95.6% vs. 94.2%). However, the overall success rate for tracing both males and females remained consistently high.

Figure V.B-7. Tracing Outcome for Transition Sample, by Sex (N = 1005)

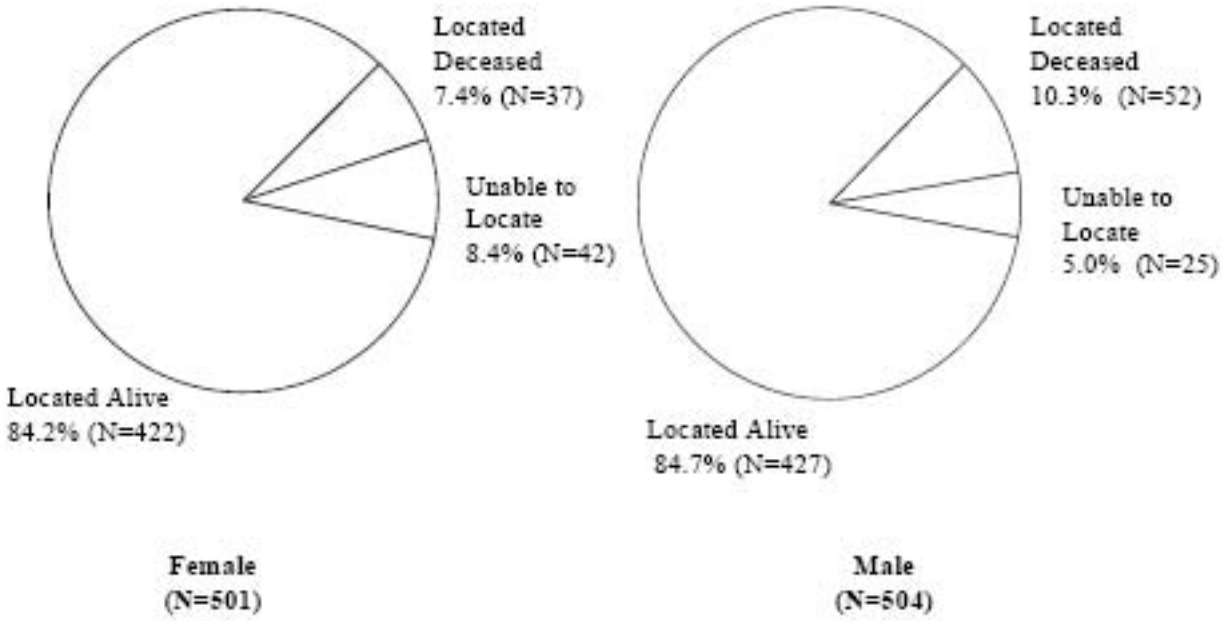
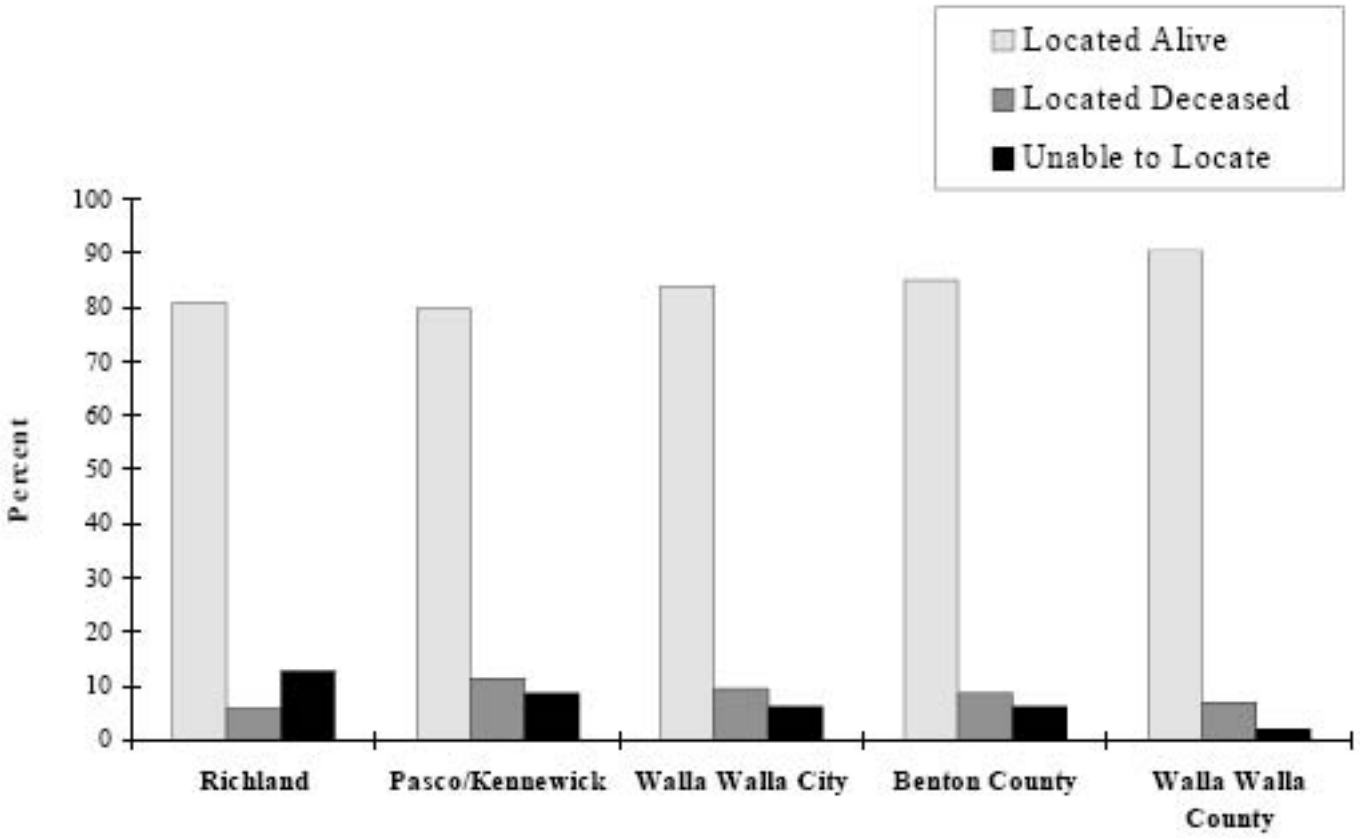


Figure V.B-8 shows tracing outcome by year of birth for the Transition Sample. Ability to locate potential participants in the Transition Sample ranged from 90.8% for those born in 1945 to 97% for those born in 1943.

Figure V.B-8. Tracing Outcome for Transition Sample, by Year of Birth (N = 1005)

Figure V.B-9 shows tracing outcomes by geostrata for the Transition Sample. The success rate for locating Transition Sample members ranged from 87.1% in the Richland geostratum to 97.8% in the Walla Walla County geostratum. As in the Pilot Study Sample, efforts were slightly more effective in locating those born in rural areas, presumably due to a less mobile population.

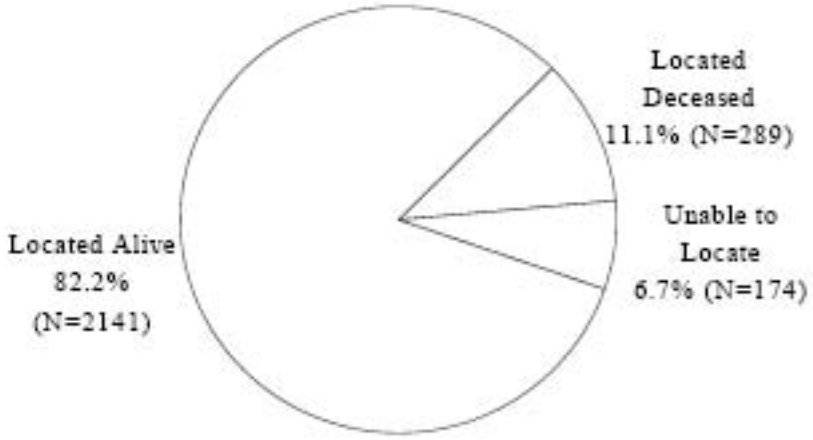
Figure V.B-9. Tracing Outcome for Transition Sample, by Geostratum (N = 1005)



B.4.c. Results for the Full Study Sample

The HTDS Full Study included all potential participants selected for the Pilot Study and Transition Samples, along with those selected later. For convenience, however, those selected after the Pilot Study and Transition Sample selections are designated the Full Study Sample. A total of 2604 potential participants were included in the Full Study Sample. The Full Study Sample was selected from five of the nine geostrata used in the entire study (Richland, Pasco/Kennewick, Benton County outside of Pasco, Franklin County outside of Kennewick, and Adams County). In addition, the Full Study Sample included people born in 1940-41. Figure V.B-10 shows tracing outcomes for the Full Study Sample. A larger percentage of Full Study Sample members were located deceased (11.1%, compared to 9.4% and 8.9% for the Pilot Study and Transition Samples), presumably due to the inclusion of potential participants born in 1940 and 1941. Nevertheless, the percentage located (93.3%) was similar to those for the Pilot Study and Transition Samples.

Figure V.B-10. Tracing Outcome for the Full Study Sample (N = 2604)



B.4.c.1. Results by Strata

Figure V.B-11 shows tracing outcomes by sex for the Full Study Sample. The percentage of female potential participants located in the Full Study Sample (91.3%) was again slightly lower when compared to the percentage of males located (95.2%). While the difference was slightly larger than for the Pilot and Transition samples, it was not substantially different.

Figure V.B-11. Tracing Outcome for the Full Study Sample, by Sex (N = 2604)

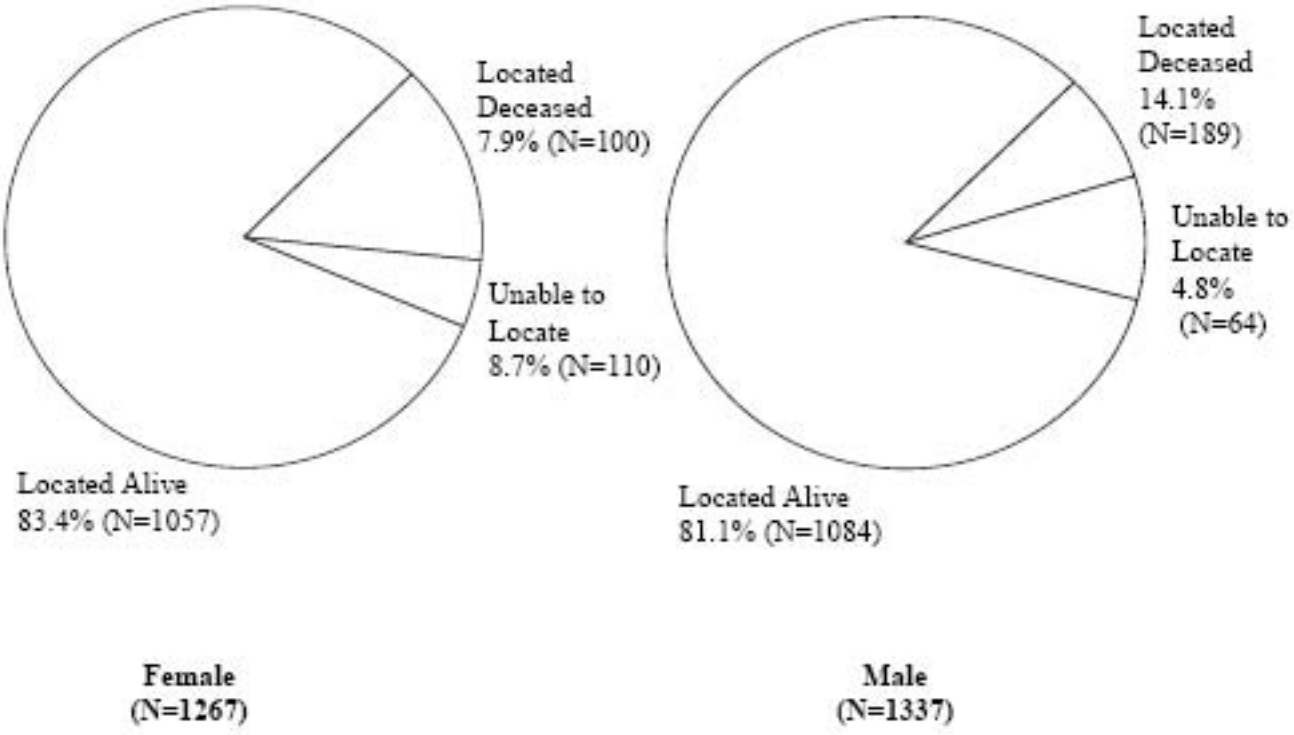


Figure V.B-12 shows tracing outcome by year of birth for the Full Study Sample. Ability to locate potential participants by year of birth in the Full Study Sample varied from 90.0% for those born in 1945 to 98.9% for those born in 1942. This is consistent with the location rates for the Pilot and Transition Samples.

Figure V.B-12. Tracing Outcome for the Full Study Sample, by Year of Birth

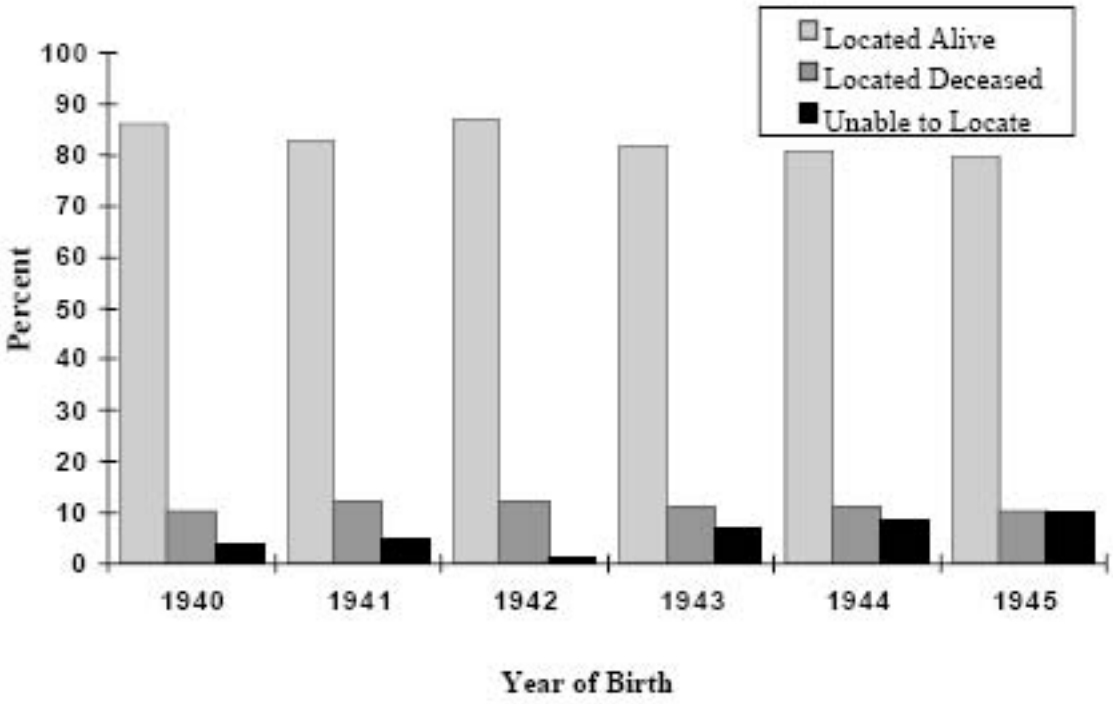
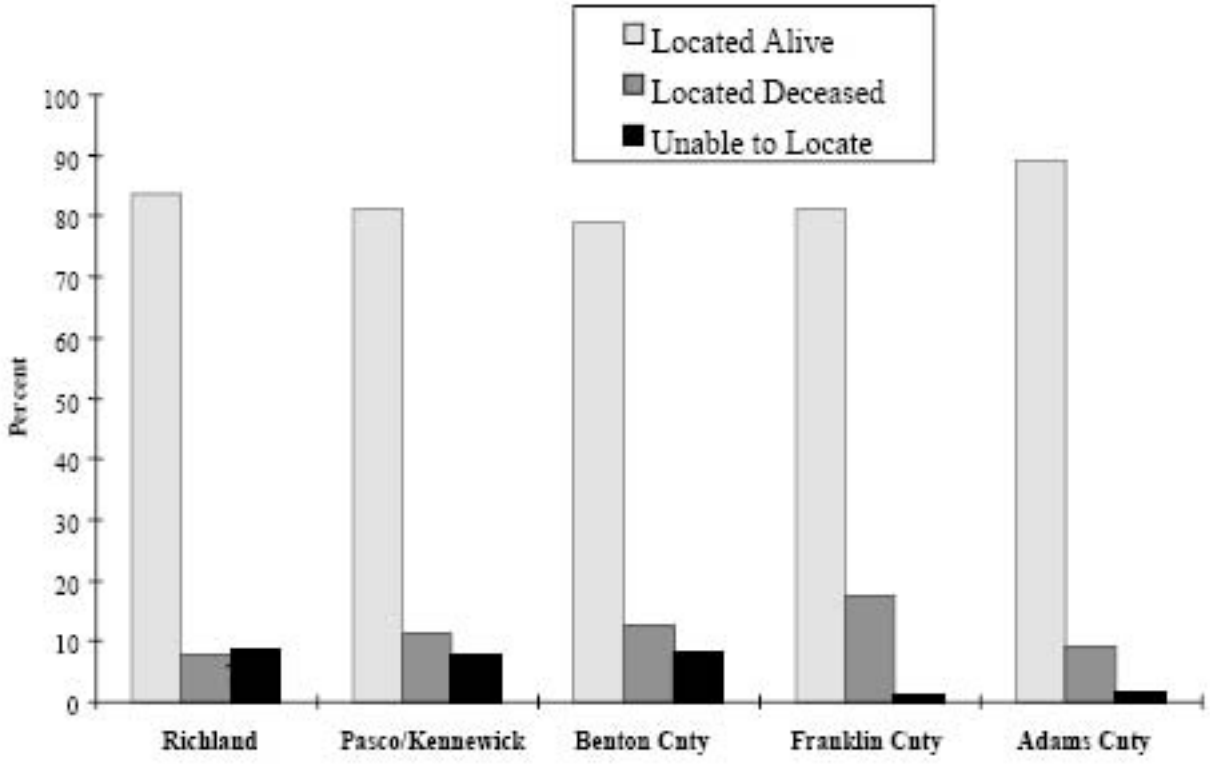


Figure V.B-13 shows tracing outcome by geostratum for the Full Study Sample. Success in locating potential participants ranged from 91.4% in the Richland geostratum to 98.6% in the Franklin County geostratum. The highest success was achieved in locating potential participants born in the relatively rural Franklin County and Adams County geostrata.

Figure V.B-13. Tracing Outcome for the Full Study Sample, by Geostratum



B.4.d. Overall Results for the Full Study

B.4.d.1. Success in Locating Study Potential Participants

Figure V.B-14 shows the final tracing outcomes for the entire study. Of the 5199 individuals sought, 4350 (83.7%) living individuals were located and 527 (10.1%) individuals were confirmed deceased. Thus, 93.8% of the sample were located and their identities confirmed. Only 322 potential participants (6.2%) remained unlocated at the end of the study. In addition, the ability to locate well over 90% of all potential participants did not vary substantially by sex, geographic region at birth, or year of birth. Figures V.B-15 to V.B-17 show the final tracing outcomes for the study by sex, by year of birth, and by geostrata.

Figure V.B-14. Final Tracing Outcomes for Entire Study (N=5199)

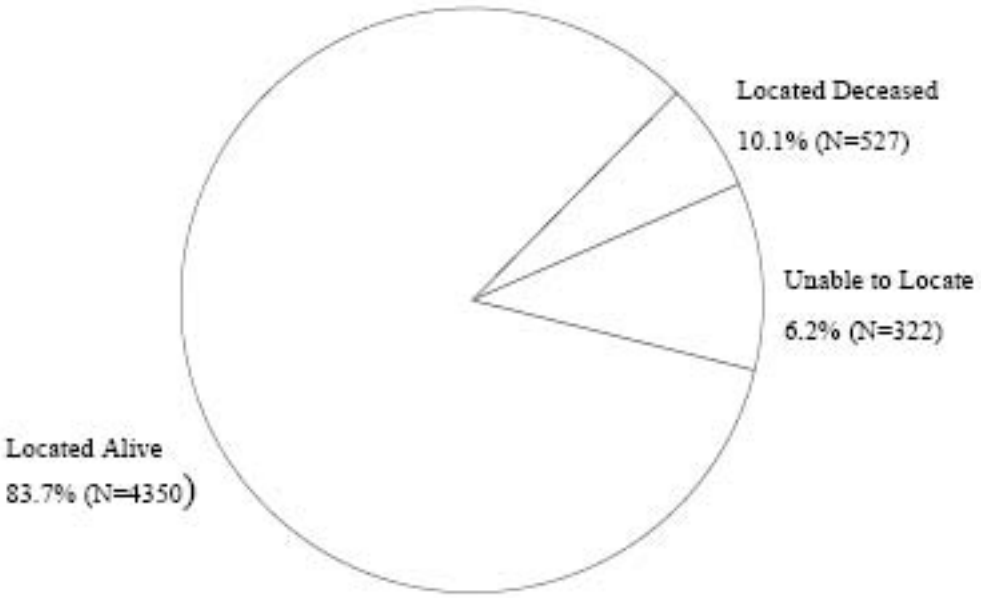


Figure V.B-15. Final Tracing Outcome for Entire Study, by Sex (N=5199)

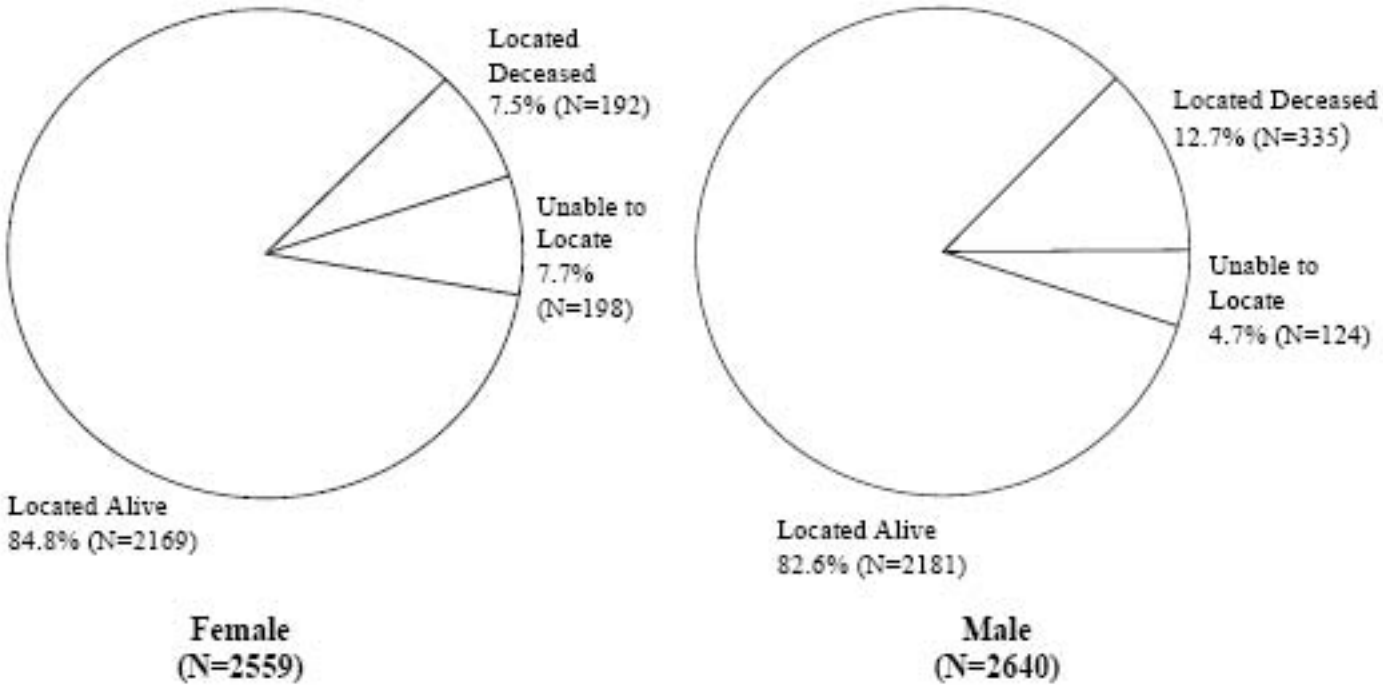


Figure V.B-16. Final Tracing Outcome for Entire Study, by Year of Birth (N=5199)

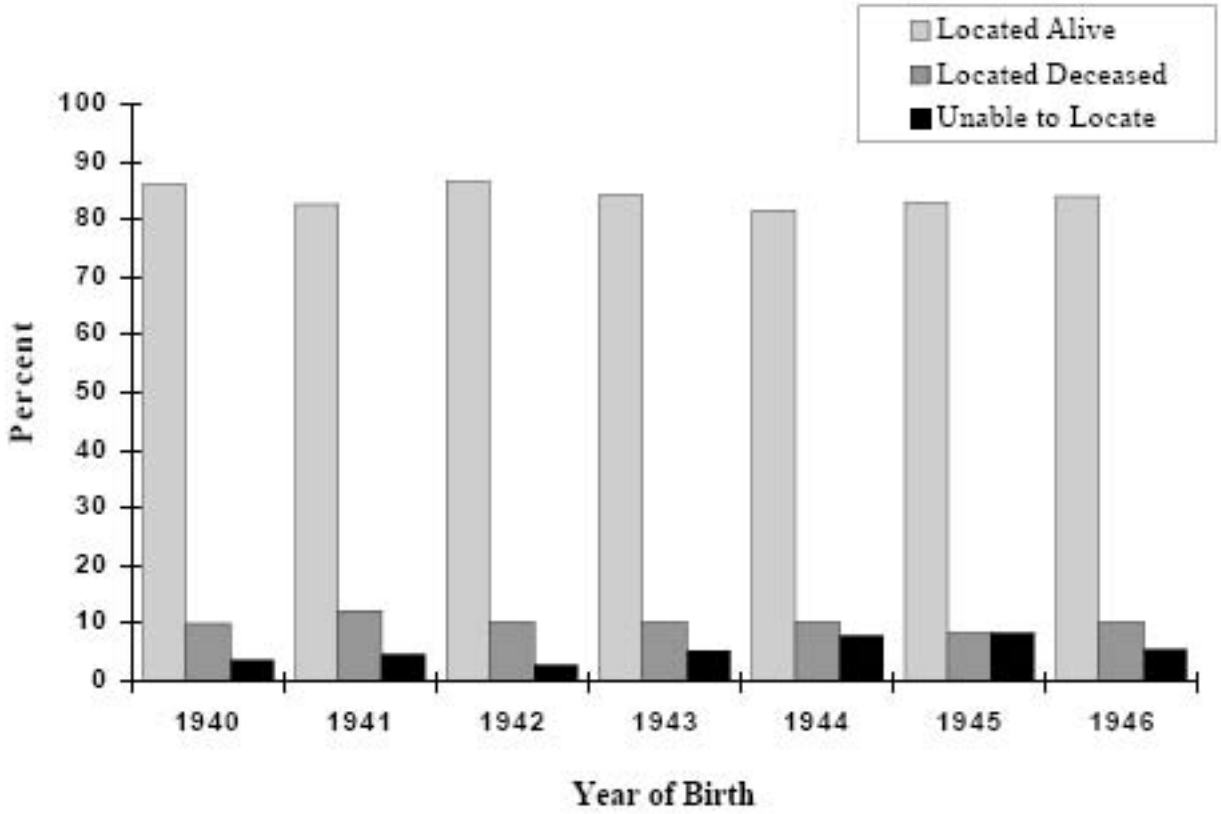
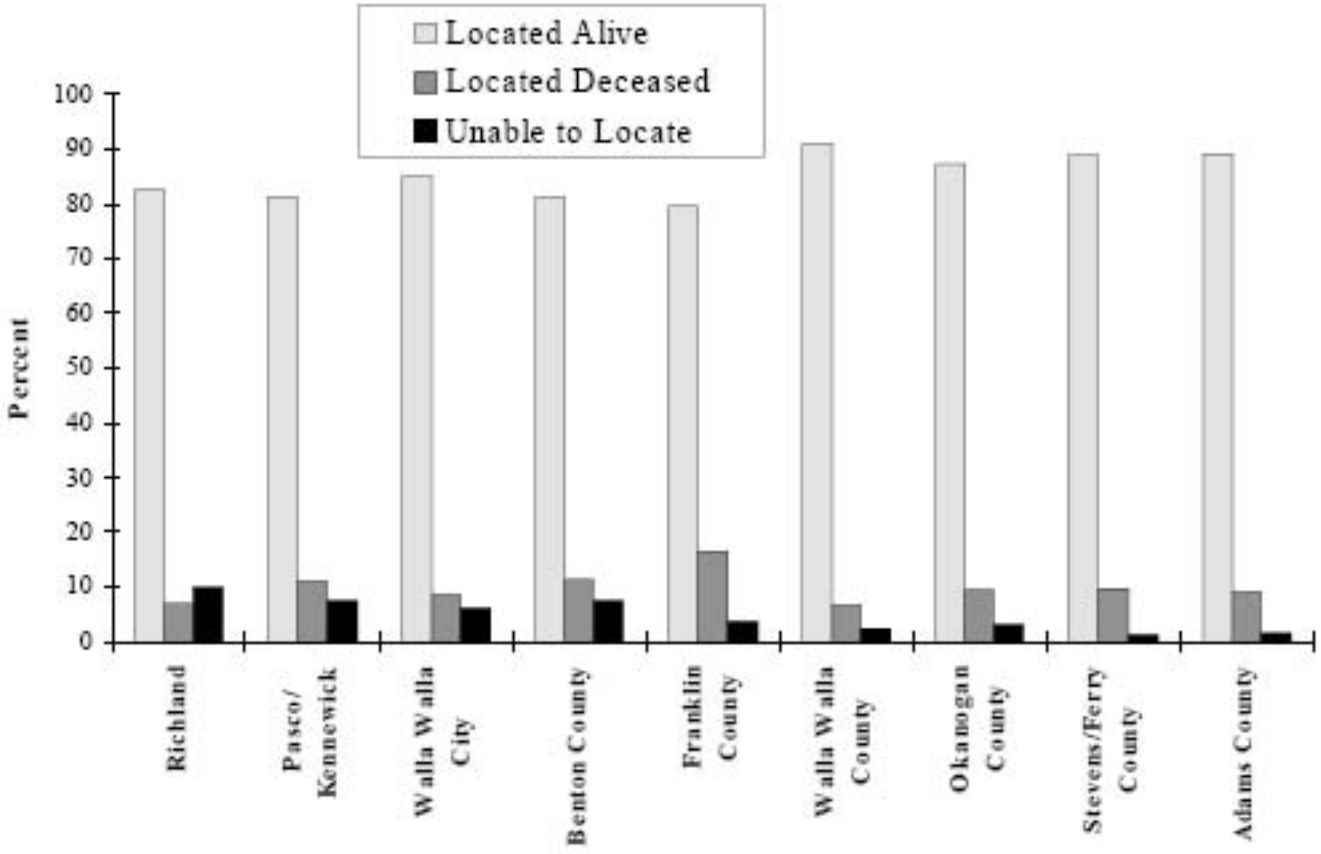


Figure V.B-17. Final Tracing Outcome for Entire Study, by Geostratum (N = 5199)



Almost 84% of all potential participants were located as living and potentially evaluable (whether they agreed to participate or not). For most (83.4%) this was confirmed directly by contact with the potential participant or with a close relative who could verify the potential participant's identity and provide a current

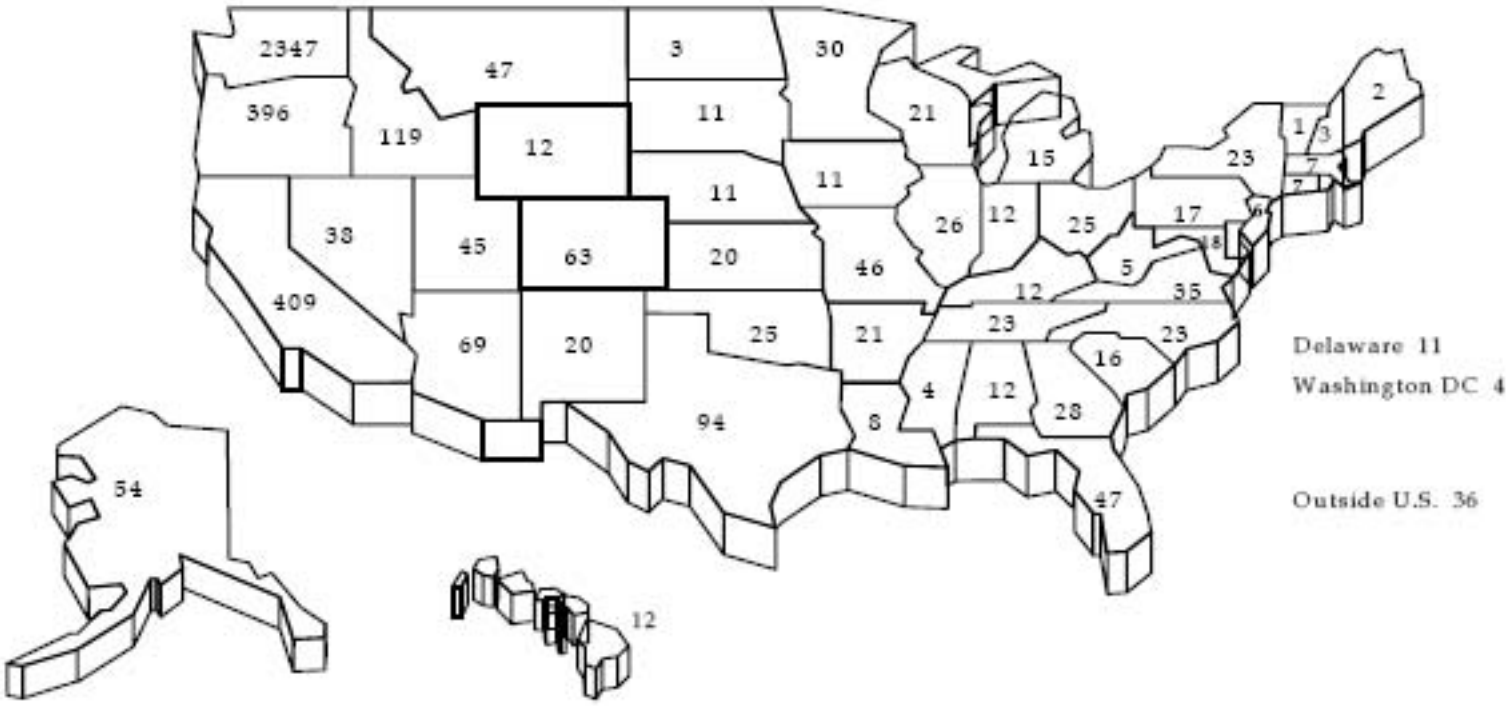
address. An additional 12 potential participants (0.2%) were located to a current address using other reliable sources providing enough information to verify their identity as the selected potential participant. These potential participants were sent a letter asking them to participate, but no direct contact was made, as no telephone number was available.

Five hundred twenty-seven (10.1%) of all selected potential participants were confirmed as deceased by a close relative and/or other reliable source (e.g., death certificate). A larger proportion of males was confirmed deceased (12.7%) than females (7.5%). Sixteen potential participants (0.3%) were located as living, but died during the study before agreeing to participate or prior to attending a clinic. An additional 22 (0.4%) potential participants were located as living but required a surrogate due to mental or physical conditions. Twenty-one of these potential participants were unable to participate in clinics, but were positively identified, while one attended a clinic with the assistance of a family member and an assistant. Two potential participants were determined to be ineligible, one because he was adopted and actually had been born in Spokane, which was his birth mother's usual residence, and the other due to a mistake on the birth certificate regarding the "Mother's Mailing Address," which indicated the mother lived in Walla Walla when the potential participant was born, when it should have been Columbia County as reflected in the "Mother's Usual Residence."

B.4.d.2. Current Residence of Living Potential Participants

At least one potential participant was located in every state in the U.S. except for Rhode Island (see Figure V.B-18). Fifty-four percent of the located potential participants resided in Washington State, 9.4% in California, 9.1% in Oregon and 2.7% in Idaho. The only other state where more than 2% of the located potential participants resided was Texas (2.2%). Thirty-six potential participants (0.8% of those located) resided outside of the U.S. Potential participants were located in Canada, Dubai, Ecuador, Germany, Mexico, Saudi Arabia, South Africa, England, Guam, Australia, Japan, France, Saipan, Hungary, Columbia, Taiwan and South Korea. Many of these (26) participated in the study. Although excessive travel costs associated with foreign travel prohibited the study from flying participants to the U.S. from outside North America, those participants who had plans to be in the U.S. during the study were brought to Seattle whenever possible to attend a clinic during that time.

Figure V.B-18. Current Residences of Located Potential Participants



B.4.d.3. Death Certificates Obtained for Deceased Potential Participants

As noted above, 527 cohort members were deceased when located, and another 16 located individuals died before agreeing to participate or attending a study clinic. For these 543 potential participants, an attempt was made to obtain a death certificate to verify the death and collect information about the cause of death. In 504 cases (92.8%), the death certificate was obtained. However, in 7.2% of cases, no death certificate could be located in the state in which the potential participant was reported to have died, or no state of death was known by the respondent, and could not be ascertained from the National Death Index. Consistent with the tracing results for living potential participants, the majority of those deceased had died in Washington State, with Oregon and California having the second and third largest proportions of deceased potential participants. Table V.B-9 shows the success in obtaining death certificates in the states where the 543 potential participants were reported to be deceased.

Table V.B-9. Summary of Death Certificates Obtained for Deceased Study Potential Participants

Reported Residence at Death	Death Certificates Obtained	Death Certificate Not Requested Due to Lack of Information	Death Certificate Requested But Not Found	Total
Washington	372	3	14	389
Oregon	30	0	1	31
California	22	0	5	27
Idaho	7	0	3	10
Montana	7	0	1	8
Texas	7	0	0	7
Colorado	6	0	0	6
Minnesota	6	0	0	6
Utah	5	0	0	5
Alaska	4	0	0	4
Nebraska	3	0	1	4
New York	3	0	1	4
Wyoming	2	0	2	4
Arizona	2	0	2	4
Nevada	3	0	0	3
Arkansas	2	0	0	2
Delaware	1	0	1	2
Florida	2	0	0	2
Georgia	2	0	0	2
Hawaii	2	0	0	2
Pennsylvania	2	0	0	2
South Carolina	2	0	0	2
Tennessee	1	0	1	2
Alabama	1	0	0	1
Illinois	1	0	0	1
Kentucky	1	0	0	1
Missouri	1	0	0	1
Mississippi	1	0	0	1
North Carolina	1	0	0	1
New Hampshire	1	0	0	1
Ohio	1	0	0	1
Oklahoma	1	0	0	1
Virginia	1	0	0	1
Out of U.S.	1	0	1	2
Unknown	0	3	0	3
Total	504	6	33	543

C. Recruiting

C.1. Background

The design of the HTDS posed significant challenges for recruiting study participants. It required that each participant be asked to identify an older relative (preferably the mother) to complete an extensive telephone interview. In addition, the participant was asked to travel to a clinic for a complete medical evaluation to determine the presence of thyroid disease and to complete an In-Person Interview.

C.1.a. Objectives of Recruiting

The objectives of the recruiting activities were to contact and obtain agreement of living potential participants to participate in the study, and to identify an appropriate Computer Assisted Telephone Interview (CATI) respondent. It was necessary to do this within a time frame that would provide sufficiently large pools of participants to schedule regional clinics, while also allowing participants ample opportunity to attend a clinic.

C.2. Recruiting Procedures

C.2.a. Initial Written Contact and Attempt to Contact by Phone

Each potential participant who was located was sent an introduction/participation letter, a study Fact Sheet and Description of Study Participation. Calls to potential participants began approximately 5-7 days after the letters were sent. Since potential participants would be in their late 40s and early 50s at the time of recruitment, they were assumed to be working. Therefore, the majority of recruitment calls were made during the evenings, taking into consideration the time zone in which the potential participant resided. A minimum of 10-15 evening attempts were made at various weeknight and weekend (generally Sunday evening) time periods, and a minimum of three daytime (weekend and weekday) calls were attempted.

If the potential participant could not be contacted by phone after 20-25 attempts, a second letter was sent explaining that the Recruiter had been unable to reach them at that phone number, and asking them to contact the Recruiter or Participation Coordinator at the toll-free HTDS number[1]. Further attempts to contact these people were postponed for approximately one month, after which both day and evening attempts would begin again until the participant was reached or until 40 attempts had been made. After 40-45 attempts resulting in no contact with either the potential participant or a household member, another letter was sent. This letter included the toll-free number and card for the potential participant to complete and return in a self-addressed stamped envelope confirming that he or she was the identified person, and asking for a phone number and time at which he or she would most likely be available.

If there was no response to this letter, and the letter was not returned with an address correction or as unable to deliver within one month, the potential participant was considered "unable to contact" and no further attempts were made. If the potential participant or household member had been reached at least once, additional attempts beyond the 40-45 calls were sometimes made, dependent on the nature of the contact.

If at any point in the process of attempting to contact a potential participant the phone number was disconnected or proved to be a wrong number, efforts were made to obtain a correct phone number through directory assistance, the original informant, or another available source. When necessary, potential

[1] If all or most calls up to this point resulted in an answering machine, a general message was left on up to three occasions explaining that we were calling from the HTDS and leaving the toll-free number for the potential participant to contact the Recruiter.

participants were returned to the tracing staff for additional tracing effort. Later in the recruitment phase, the FHCRC Tracking Resource Center assisted in locating updated address and telephone information. If a new telephone number could not be obtained, a second letter (as described above for those not contacted after 20-25 attempts) was sent asking the potential participant to contact HTDS at the toll-free number. If no response was received and no telephone contact was ever made, a letter was sent, asking him or her to contact the study or return the enclosed card to confirm identity as the study potential participant and/or providing contact information.

C.2.b. Telephone Contact with the Potential Participant

Once the potential participant was reached by phone, the Recruiter explained the reason for the call, confirmed the person's identity (full name, date and county of birth) and attempted to obtain agreement to participate by explaining the purpose and nature of the study and responding to any concerns as appropriate. A script was developed and used to ensure that each potential participant received the same basic information about the study. However, the nature of the recruitment call required that Recruiters be flexible enough to respond to individual questions and concerns. Recruiters were trained to be able to address a variety of questions and concerns in order to obtain the highest participation rate possible.

Every effort was made to recruit and provide interpreters or other assistance as necessary for non-English speakers, illiterate, hearing and vision impaired, or otherwise impaired persons to achieve maximum participation in the study. If a potential participant was reluctant to participate, the Recruiter would encourage him or her to contact the Participation Coordinator or Project Manager so that specific concerns could be addressed. If the potential participant still refused, in most cases, a second contact by letter was sent in approximately three to six months to allow for the possibility that he or she would have reconsidered the decision. This letter was followed by a telephone call, as with the first attempt, to try again to gain participation and to respond to any questions or concerns.

If the potential participant agreed to participate in the study, the Recruiter requested that the participant name a respondent for the CATI. Whenever possible, the CATI respondent was the potential participant's mother, who was assumed to be best able to answer the CATI questions. The next choices, in order of preference were: father, older sibling (at least six years older), or other family member who lived with the potential participant for a large part of his/her early childhood since birth.

The Recruiter described the dosimetry materials and interview to ensure that the participant felt that the respondent would be willing and able to complete the CATI process. A CATI Respondent Assessment (Appendix 4) was then completed with the participant. Questions were asked about the respondent's abilities, such as sight, hearing and special needs. This information was then provided to the CATI Interviewer.

If no CATI respondent was available, the potential participant was informed that he or she was still eligible for participation and was assured that his or her participation was valuable even without a CATI respondent. Participants without a CATI respondent were interviewed at the clinic using an expanded version of the In-Person Interview (IPI).

During the recruitment call, the Recruiter assessed whether travel arrangements were required and which clinic site would be the most accessible for the participant. In most cases, the clinic site selected was the one closest to the participant's usual residence. Seattle was selected as the clinic location for most participants living outside of the Pacific Northwest, for both participant convenience and typically lower airfare cost.

If a CATI respondent was named, the participant was called back after the CATI was completed to schedule the clinic visit. If no CATI respondent was named, attempts to schedule could begin immediately, depending on availability at the clinic location selected.

C.2.c. Confirmation of Agreement to Participate and Six Month Letter

In the Pilot Study, letters were sent to participants soon after they had agreed to participate, thanking them for agreeing to participate and explaining that they would be contacted to schedule a clinic appointment. During the Full Study, when the volume of letters to participants was extremely high and lag time between recruiting and scheduling could be six months or longer, the confirmation letter was replaced by a letter sent to all participants who had not yet been scheduled for a clinic within six months after the recruitment call. The purpose of the "six month letter" was two-fold. First, it served to assure participants that they would be contacted and that their participation was still very important to the study. Second, it enabled the study to be advised of address changes through the United States Postal Service change of address service.

C.2.d. Refusals and Second Attempts

While every reasonable effort was made to persuade each potential participant to participate, it was inevitable that some would refuse or be unable to participate. When a potential participant refused, the Recruiter asked them to complete a Refusal/Demographic Questionnaire (Appendix 5). Twelve demographic questions relating to race, ethnic origin, income, religion, and education level were asked to obtain a general profile of those who refused to participate or later withdrew from the study.

The Recruiter also completed a Refusal Assessment (Appendix 6) after the call to record the nature and strength of the refusal from the Recruiter's perspective. This information was used to determine if, and when, to re-contact the potential participant to have the best opportunity to convert the refusal to an agreement to participate. A second attempt to recruit was generally made unless the participant specifically requested that the HTDS not re-contact them, was hostile, or if it was clearly not possible for this person to participate in the study for reasons such as long term illness or disability. The default date for making second attempts was set at approximately three months after the first attempt.

C.2.e. Second Request for Participation

A second attempt letter, requesting participation and explaining the study, was sent within three to six months following the first recruitment contact, or after an appropriate amount of time based on information provided by the potential participant and the Recruiter. As with the initial contact, each letter also included a description of study participation and fact sheets. A Recruiter began attempts to call approximately 5-7 days after the second letter was sent. As with the first attempt call, a script was used as a guideline to ensure that all potential participants received the same information about the study. However, as with the initial attempt, the Recruiter's approach and responses were individualized to respond to the potential participant's questions and concerns.

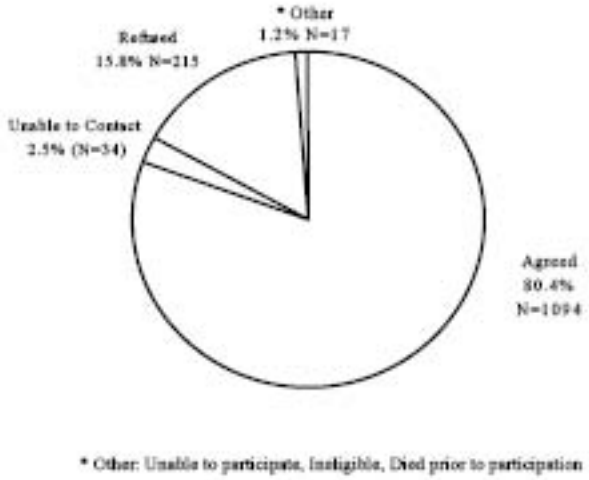
If the potential participant agreed to participate on the second attempt, the same steps were followed as for an agreement on the first attempt in requesting CATI respondent information and determining clinic location. If he or she refused, the Recruiter asked him or her to complete a Refusal Demographic Questionnaire (unless this had been completed during the first attempt call). The Recruiter also completed a Refusal Assessment after the call to record the reason for and strength of the refusal. No further recruitment attempts were made if a potential participant refused on the second attempt.

C.3. Outcome and Results

C.3.a. Results for the Pilot Study Sample

Figure V.C-1 summarizes the willingness of individuals in the Pilot Study Sample to agree to participate in the study. It should be noted that these numbers may vary slightly from those found in the Pilot Study Final Report of January 24, 1995, as some additional participants from the Pilot Study Sample were recruited after that time.

Figure V.C-1. Agreement to Participate for the Pilot Study Sample (N = 1360)



Of the 1360 potential participants located alive, 1354 (99.6%) were sent letters requesting participation, and 1320 (97.1%) were contacted by telephone. One thousand ninety-four (80.4%) of those located alive agreed to participate (82.9% of those contacted by telephone). Eleven of those located alive were judged physically incapable of participating by a close relative or guardian, or were found to be otherwise unable to participate. Two hundred fifteen (15.8%) of the living located potential participants refused to participate in the study. Of those agreeing to participate, 49 (3.6%) refused on the initial attempt, but were re-contacted a second time and the refusal was converted to agreement. The participation rate remained remarkably constant over the course of the Pilot Study, fluctuating less than 3% in either direction over the last year of this phase of the study. Table V.C-1 summarizes the recruiting experience for the Pilot Study Sample.

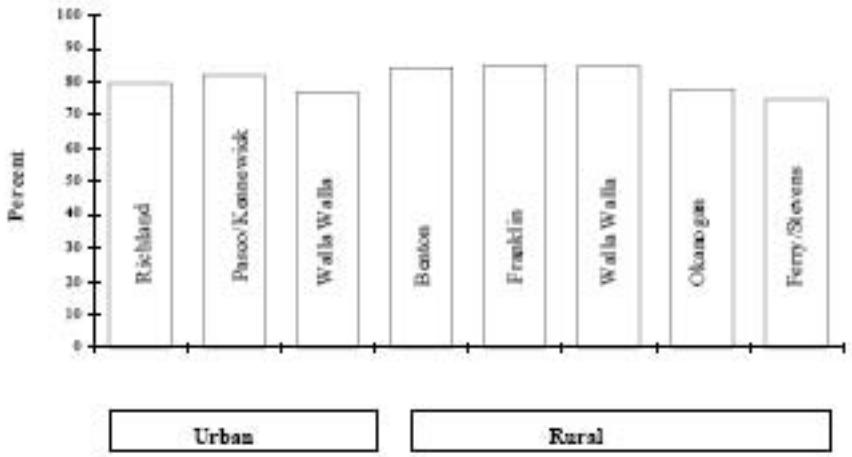
Table V.C-1. Summary of Agreement and Refusal for the Pilot Study Sample (N=1360)

Contact Status	No.	% of Contacted by Phone	% of Letter Sent	% of Total
Letter sent	1354	--	100.0	99.6
Unable to contact	34	--	2.5	2.5
Contacted by phone	1320	100.0	97.5	97.1
Agreed, final	1094	82.9	80.8	80.4
- on first attempt	1045	79.2	77.2	76.8
- on second attempt	49	3.7	3.6	3.6
Refused, final	215	16.3	15.9	15.8
Unable to participate	11	0.8	0.8	0.8
Died prior to participation	4	--	--	0.3
Ineligible	2	--	--	0.1
Located with no contact	0	--	--	0.0

In summary, the Pilot Study demonstrated that, once located and contacted by telephone, a large proportion of individuals would agree to participate in the study. Approximately 83% of those in the Pilot Study Sample who were contacted by telephone agreed to participate during the course of the study.

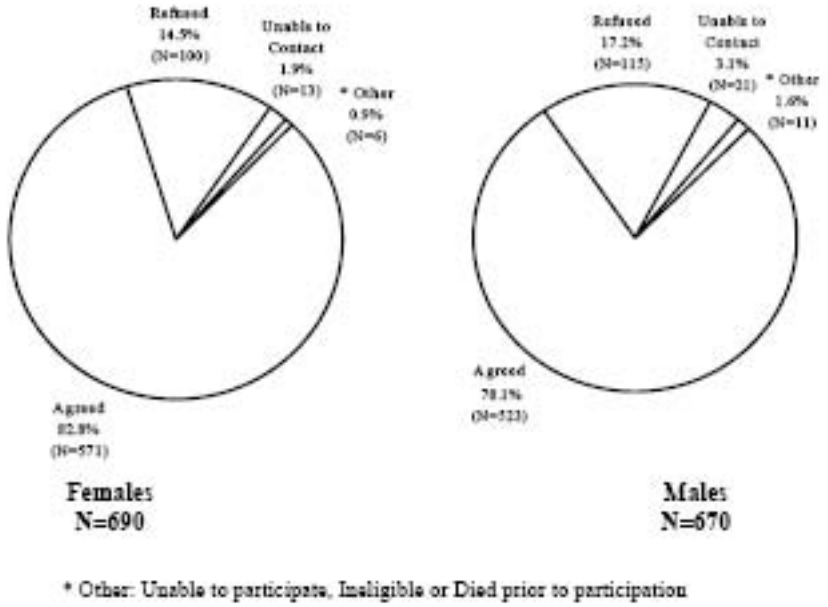
Figure V.C-2 shows the proportion of the Pilot Study Sample located alive who agreed to participate, by the eight geostrata used in the Pilot Study. The participation rate was uniformly high and relatively similar across the eight geostrata. The lowest percentage was among those born in Ferry and Stevens counties, located furthest from the Hanford Site (74.5%), and the highest was in Franklin County (84.9%), the area closest to the site.

Figure V.C-2. Agreement to Participate for the Pilot Study Sample, by Geostratum (N=1360)



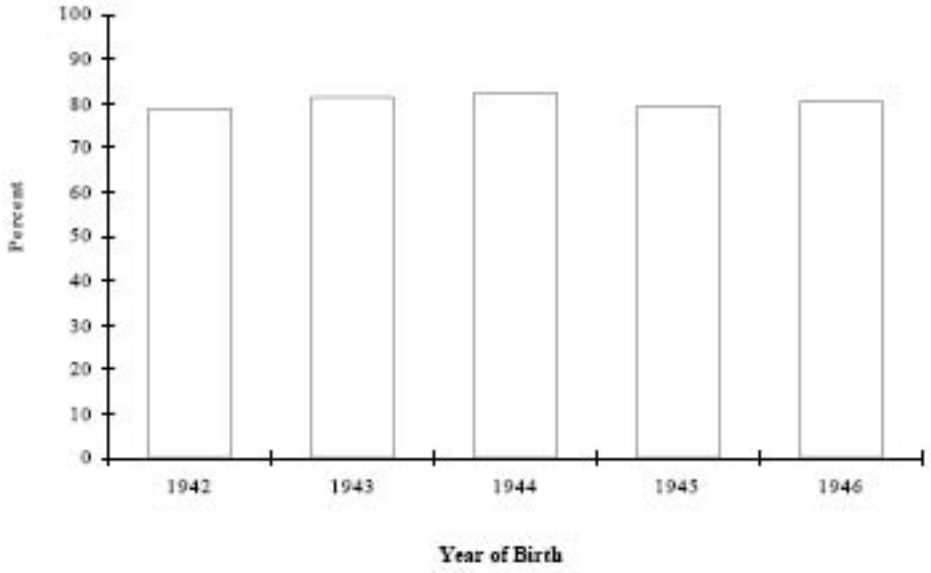
Figures V.C-3 and V.C-4 show that willingness to participate also did not differ substantially according to sex (82.8% for females vs. 78.1% for males) or year of birth (78.8% to 82.4%).

Figure V.C-3. Agreement to Participate for the Pilot Study Sample, by Sex (N = 1360)



* Other: Unable to participate, Ineligible or Died prior to participation

Figure V.C-4. Agreement to Participate for the Pilot Study Sample, by Year of Birth (N = 1360)



Similarly, the area of current residence did not significantly influence the willingness to participate. The most common reasons for non-participation were "Not Interested" and "No Time," with 64.7% (139) of refusals and withdrawals falling into these two categories. The next most common reason for non-participation was illness or medical impairment/disability. Eighteen (8.4%) Pilot Study non-participants or their family member/guardian cited a medical condition, illness, disability, or impairment as the reason for not participating. Surprisingly, unwillingness to travel was only cited as the reason for non-participation by four potential participants outside the Northwest in the Pilot Study Sample. Other reasons given were opposition to the study, concern about the effect of participation on insurance coverage, advice from an attorney, and not having thyroid disease. Table V.C-2 shows the reasons for refusal or withdrawal from the study by geographic area of current residence for the Pilot Study Sample.

Table V.C-2. Reason for Refusal/Withdrawal for the Pilot Study Sample by Geographic Area of Current Residence (N=215)

Area of Current Residence	Reason for Refusal or Withdrawal														
	Not Interested or No Time		Illness or Impairment		Unwilling to Travel		Opposed to Study		Legal or Insurance Concerns		No Thyroid Disease		Other*		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
All WA	82	66.1	9	7.3	1	0.8	8	6.5	3	2.4	1	0.8	20	16.1	124
Seattle	12	75.0	1	6.2	0	--	0	--	0	--	0	--	3	18.8	16
Everett	1	33.3	0	--	0	--	1	33.3	0	--	0	--	1	33.3	3
Tacoma	3	60.0	0	--	0	--	0	--	0	--	0	--	2	40	5
Olympia	3	75.0	0	--	0	--	0	--	0	--	0	--	1	25.0	4
SW WA	5	83.3	0	--	0	--	1	16.7	0	--	0	--	0	--	6
Wenatchee	9	69.2	3	23.1	0	--	0	--	0	--	0	--	1	7.7	13
Yakima	2	25.0	1	12.5	1	12.5	0	--	1	12.5	0	--	3	37.5	8
Spokane	22	75.9	0	--	0	--	3	10.3	0	--	1	3.4	3	10.3	29
Tri-Cities	24	61.5	4	10.3	0	--	3	7.7	2	5.1	0	--	6	15.4	39
SE WA	1	100	0	--	0	--	0	--	0	--	0	--	0	--	1
Other NW	21	60.0	3	8.6	1	2.9	2	5.7	2	5.7	1	2.9	5	14.3	35
CA/HI	9	52.9	5	29.4	0	--	1	5.9	1	5.9	0	--	1	5.9	17
Southwest	11	91.7	0	--	0	--	0	--	0	--	0	--	1	8.3	12
Midwest	7	58.3	1	8.3	4	33.3	0	--	0	--	0	--	0	--	12
South	7	70.0	0	--	0	--	0	--	0	--	0	--	3	30.0	10
East	2	40.0	0	--	0	--	1	20.0	0	--	1	20.0	1	20.0	5
Other	0	--	0	--	0	--	0	--	0	--	0	--	0	--	0
Total	139	64.7	18	8.4	6	2.8	12	5.6	6	2.8	3	1.4	31	14.4	215

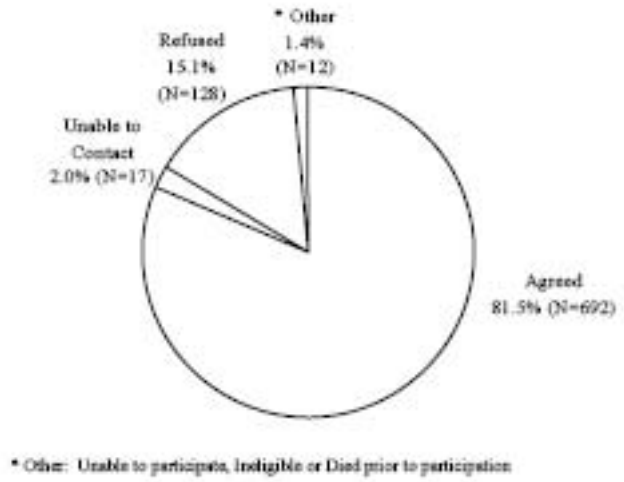
* Other: Includes family problems, personal reasons, distrust, lack of personal benefit, scheduling problems, refusal by a household member on the potential participant's behalf, and no reason given.

Overall, these results indicate that the methods developed for recruiting participants for the study were feasible and would result in relatively high levels of participation.

C.3.b. Results from the Transition Sample

Figure V.C-5 summarizes the willingness of individuals in the Transition Sample to agree to participate during the course of the study.

Figure V.C-5. Agreement to Participate for the Transition Sample (N = 849)



Of the 849 potential participants located alive, 847 (99.8%) were sent letters requesting participation, and 831 (97.9%) were contacted by telephone. Six hundred ninety-two (81.5%) of those located alive agreed to participate. Eleven located potential participants were judged medically incapable of participating by a close relative or guardian contacted during the process, or were found to be otherwise unable to participate. One hundred twenty-eight of those located alive (15.1%) refused to participate in the study. Of those agreeing to participate, 33 (3.9%) potential participants refused on the initial attempt, but were re-contacted a second time and agreed to participate on the second recruiting attempt. Sixteen (1.9%) of those located to an address were unreachable by telephone and could not be recruited. Table V.C-3 summarizes the recruiting experience for the Transition Sample.

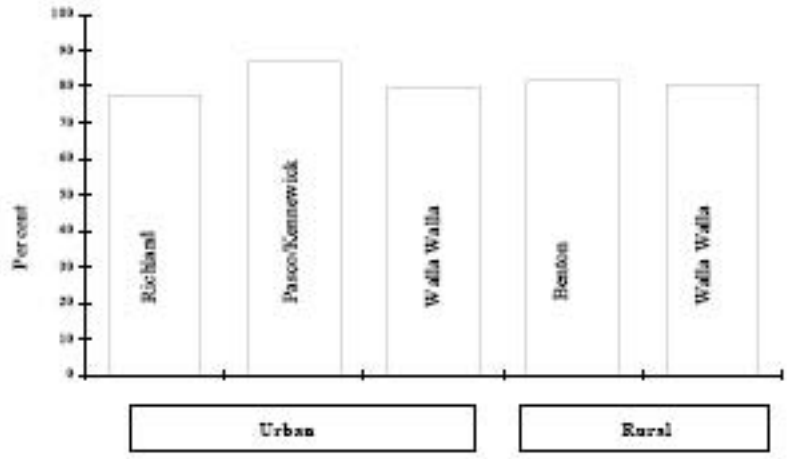
Table V.C-3. Summary of Agreement and Refusal for theTransition Sample (N=849)

Contact Status	No.	% of Contacted by Phone	% of Letter Sent	% of Total
Letter sent	847	--	100.0	99.8
Unable to contact	16	--	1.9	1.9
Contacted by phone	831	100.0	98.1	97.9
Agreed, final	692	83.3	81.7	81.5
- on first attempt	659	79.3	77.8	77.6
- on second attempt	33	4.0	3.9	3.9
Refused, final	128	15.4	15.1	15.1
Unable to participate	11	1.3	1.3	1.3
Died prior to participation	1	--	--	0.1
Ineligible	0	--	--	0.0
Located with no contact	1	--	--	0.1

In summary, the results in the Transition Sample did not differ appreciably from those in the Pilot Study. Of those individuals contacted by telephone, 83.3% agreed to participate in the study. A total of 2.0% (17) of those located to an address were not reachable by telephone.

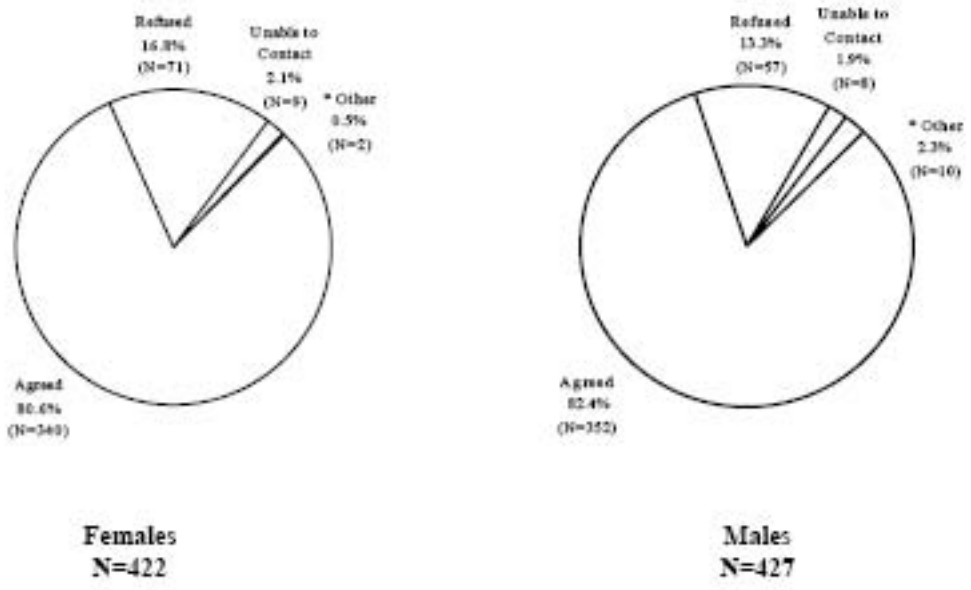
Figure V.C-6 shows the proportion of Transition Sample potential participants located alive who agreed to participate, according to the five geostrata used in the Transition Sample. The participation rate was uniformly high and relatively similar across the five areas. The lowest percentage was among those born in Richland (77.6%), and the highest among those born in Pasco/Kennewick (86.7%).

Figure V.C-6. Agreement to Participate for the Transition Sample, by Geostratum (N=849)



Willingness to participate did not differ substantially according to sex (80.6% of females vs. 82.4% of males) or year of birth (78.7% to 86.3%) (Figures V.C-7 and V.C-8). Similarly, the area of current residence did not significantly influence the willingness to participate. Table V.C-4 summarizes the reasons for refusal by geographic area of current residence for the Transition Sample. Reasons for refusal did not vary substantially from the Pilot Study Sample experience.

Figure V.C-7. Agreement to Participate for the Transition Sample, by Sex (N=849)



* Other: Unable to participate, Ineligible or Died prior to participation

Figure V.C-8. Agreement to Participate for the Transition Sample, by Year of Birth (N=849)

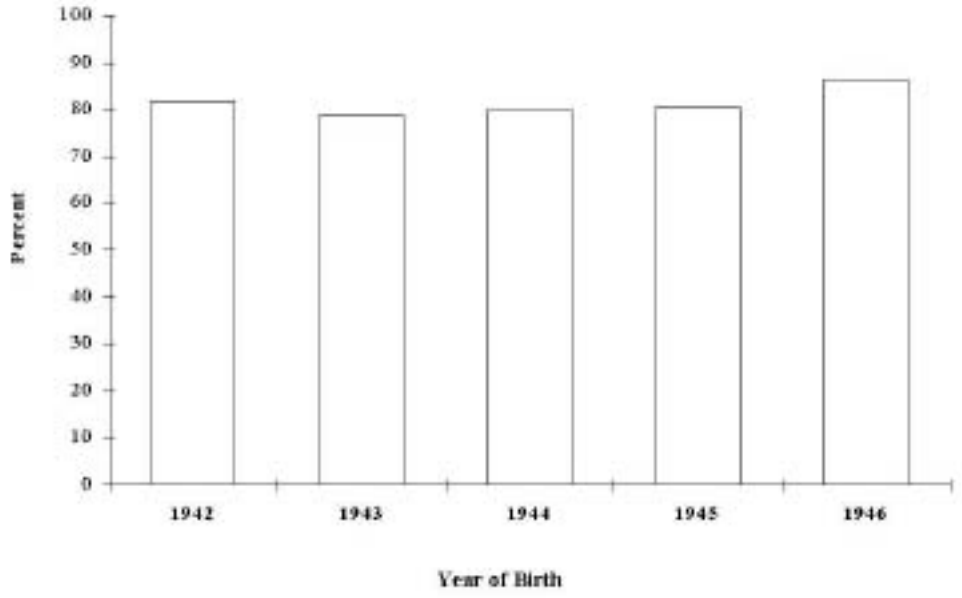


Table V.C-4. Reason for Refusal/Withdrawal for the Transition Sample, by Geographic Area of Current Residence (N=128)

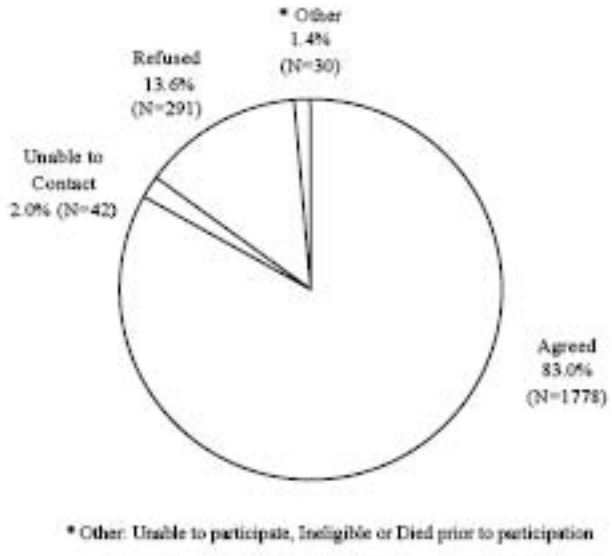
Area of Current Residence	Reason for Refusal or Withdrawal														
	Not Interested or No Time		Illness or Impairment		Unwilling to Travel		Opposed to Study		Legal Concerns		No Thyroid Disease		Other*		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
All WA	48	69.6	3	4.3	0	--	4	5.8	1	1.4	1	1.4	12	17.4	69
Seattle	6	60.0	0	--	0	--	0		0	--	0	--	4	40.0	10
Everett	2	100	0	--	0	--	0	--	0	--	0	--	0	--	2
Tacoma	2	100	0	--	0	--	0	--	0	--	0	--	0	--	2
Olympia	4	80.0	1	20.0	0	--	0	--	0	--	0	--	0	--	5
SW WA	1	33.3	0	--	0	--	1	33.3	0	--	0	--	1	33.3	3
Wenatchee	2	100	0	--	0	--	0	--	0	--	0	--	0	--	2
Yakima	4	57.1	1	14.3	0	--	1	14.3	1	14.3	0	--	0	--	7
Spokane	5	71.4	0	--	0	--	1	14.3	0	--	0	--	1	14.3	7
Tri-Cities	22	71.0	1	3.2	0	--	1	3.2	0	--	1	3.2	6	19.4	31
SE WA	0	--	0	--	0	--	0	--	0	--	0	--	0	--	0
Other NW	9	56.2	1	6.2	1	6.2	0	--	0	--	0	--	5	31.2	16
CA/HI	6	66.7	1	11.1	1	11.1	0	--	0	--	0	--	1	11.1	9
Southwest	2	50.0	0	--	1	25.0	1	25.0	0	--	0	--	0	--	4
Midwest	8	66.7	1	8.3	0	--	0	--	0	--	1	8.3	2	16.7	12
South	6	75.0	0	--	1	12.5	0	--	0	--	0	--	1	12.5	8
East	6	66.7	0	--	0	--	0	--	0	--	0	--	3	33.3	9
Other	0	--	0	--	0	--	0	--	0	--	0	--	1	100	1
Total	85	66.4	6	4.7	4	3.1	5	3.9	1	0.8	2	1.6	25	19.5	128

* Other: Includes family problems, personal reasons, distrust, lack of personal benefit, scheduling problems, refusal by a household member on the potential participant's behalf, and no reason given.

C.3.c. Results for the Full Study Sample

Figure V.C-9 summarizes the willingness of those located alive in the Full Study Sample to agree to participate during the course of the study.

Figure V.C-9. Agreement to Participate for the Full Study Sample (N = 2141)



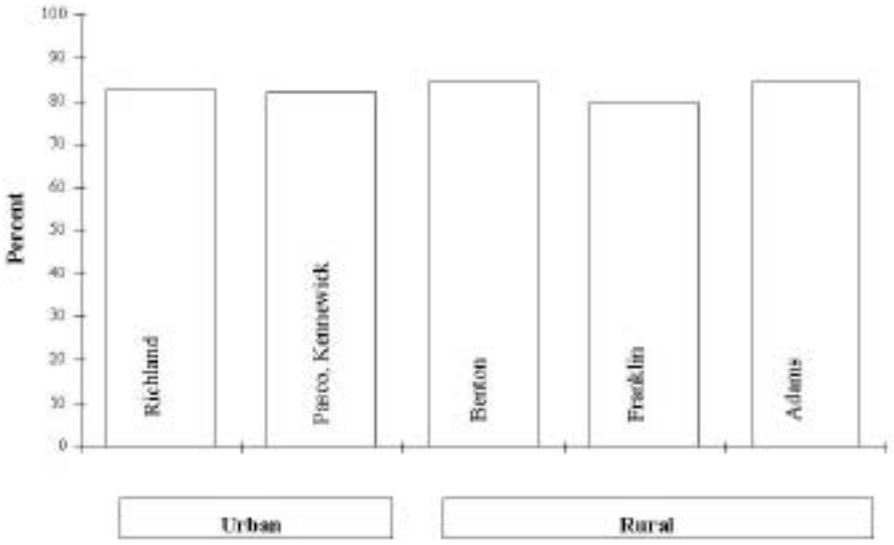
Of the 2141 Full Study Sample potential participants located alive, 2128 (99.4%) were sent letters requesting participation, and 2088 (97.5%) were contacted by telephone. A total of 1778 (83.0%) of those located alive agreed to participate. Nineteen (0.9%) of those located alive were judged medically incapable of participating by a close family member or guardian, or were found to be otherwise unable to participate. Two hundred ninety-one of those located alive (13.6%) refused to participate in the study. Of those agreeing to participate, 36 (1.7%) refused on the initial attempt, but were re-contacted a second time, and agreed to participate on the second recruiting attempt. Forty-two (2.0%) of those located to an address were unreachable by telephone. Table V.C-5 summarizes the recruiting experience for the Full Study Sample.

Table V.C-5. Summary of Agreement and Refusal for the Full Study Sample (N=2141)

Contact Status	No.	% of Contacted by Phone	% of Letter Sent	% of Total
Letter Sent	2128	--	100.0	99.4
Unable to contact	40	--	1.9	1.9
Contacted by phone	2088	100.0	98.1	97.5
Agreed, final	1778	85.2	83.6	83.0
- on first attempt	1742	83.4	81.9	81.4
- on second attempt	36	1.7	1.7	1.7
Refused, final	291	13.9	13.7	13.6
Unable to participate	19	0.9	0.9	0.9
Died prior to participation	11	--	--	0.5
Ineligible	0	--	--	0.0
Located with no contact	2	--	--	0.1

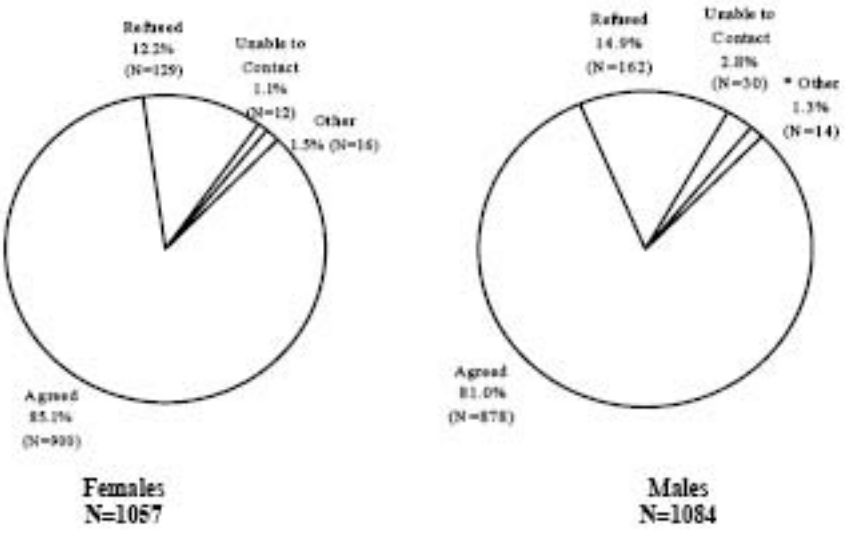
Figure V.C-10 shows the proportion of Full Study Sample members located alive who agreed to participate in the study, according to the five geostrata used in the Full Study Sample. The participation rate was uniformly high and relatively similar across the areas. The lowest percentage was among those born in Franklin County (80.0%), while the highest was among those born in Benton County (84.4%).

Figure V.C-10. Agreement to Participate for the Full Study Sample, by Geostratum (N=2141)



Willingness to participate also did not differ substantially according to sex (85.1% for females vs. 81.0% for males) or year of birth (77.5% to 89.6%) (Figures V.C-11 and V.C-12). Similarly, the area of current residence did not significantly influence the willingness to participate. Table V.C-6 shows the reasons for non-participation by geographic area of current residence. Reasons given were similar to those given in the Pilot and Transition Samples.

Figure V.C-11. Agreement to Participate for the Full Study Sample, by Sex (N = 2141)



* Other: Unable to participate, Ineligible or Died prior to participation

Figure V.C-12. Agreement to Participate for the Full Study Sample, By Year of Birth (N=2141)

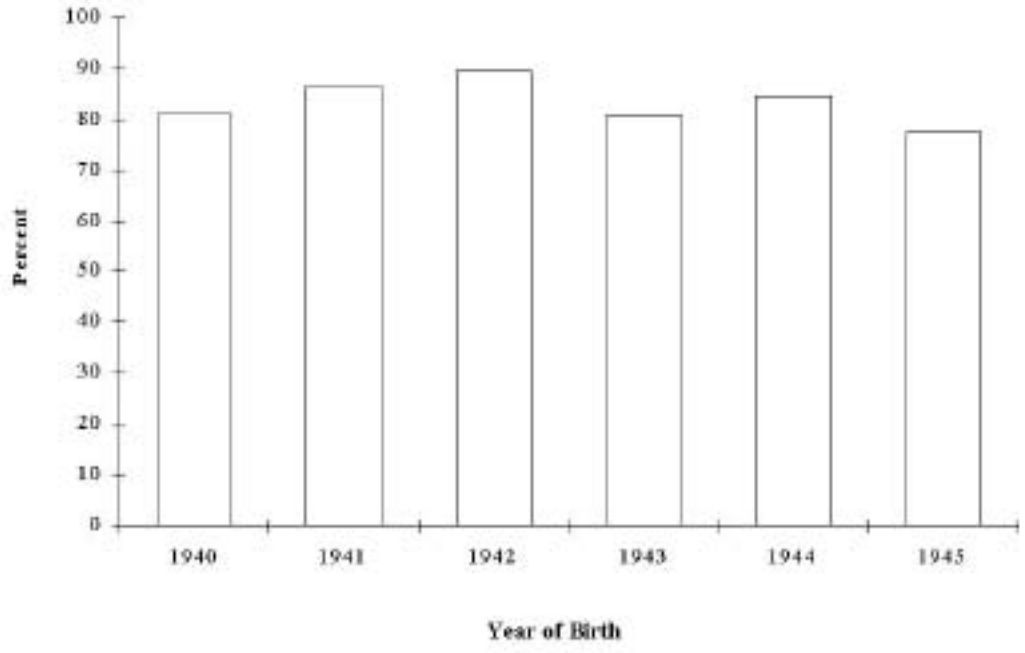


Table V.C-6. Reason for Refusal/Withdrawal for the Full Study Sample, by Geographic Area of Current Residence (N=291)

Area of Current Residence	Reason for Refusal or Withdrawal														
	Not Interested or No Time		Illness or Impairment		Unwilling to Travel		Opposed to Study		Insurance Concerns		No Thyroid Disease		Other*		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
All WA	86	64.2	9	6.7	2	1.5	5	3.7	1	0.7	0	--	31	23.1	134
Seattle	10	55.6	1	5.6	0	--	1	5.6	1	5.6	0	--	5	27.8	18
Everett	4	57.1	1	14.3	0	--	0	--	0	--	0	--	2	28.6	7
Tacoma	6	75.0	0	--	0	--	0	--	0	--	0	--	2	25.0	8
Olympia	3	50.0	1	16.7	1	16.7	0	--	0	--	0	--	1	16.7	6
SW WA	6	66.7	0	--	0	--	1	11.1	0	--	0	--	2	22.2	9
Wenatchee	8	88.9	0	--	0	--	0	--	0	--	0	--	1	11.1	9
Yakima	8	72.7	1	9.1	0	--	0	--	0	--	0	--	2	18.2	11
Spokane	12	60.0	3	15.0	0	--	0	--	0	--	0	--	5	25.0	20
Tri-Cities	29	63.0	2	4.3	1	2.2	3	6.5	0	--	0	--	11	23.9	46
SE WA	0	--	0	--	0	--	0	--	0	--	0	--	0	--	0
Other NW	21	55.3	5	13.2	3	7.9	0	--	0	--	1	2.6	8	21.1	38
CA/HI	20	71.4	2	7.1	3	10.7	1	3.6	0	--	0	--	2	7.1	28
Southwest	17	63.0	5	18.5	1	3.7	2	7.4	0	0	0	0	2	7.4	27
Midwest	19	70.4	2	7.4	3	11.1	0	--	0	--	0	--	3	11.1	27
South	13	56.5	0	--	7	30.4	0	--	0	--	0	--	3	13.0	23
East	10	83.3	1	8.3	0	--	0	--	0	--	0	--	1	8.3	12
Other	1	50.0	0	--	1	50.0	0	--	0	--	0	--	0	--	2
Total	187	64.3	24	8.2	20	6.9	8	2.7	1	0.3	1	0.3	50	17.2	291

* Other: Includes family problems, personal reasons, distrust, lack of personal benefit, scheduling problems, refusal by a household member on the potential participant's behalf, and no reason given.

C.3.d. Results for the Entire Study

A summary of the agreement to participate for the entire study is provided in Table V.C-7 and shown in Figure V.C-13. In all, 4239 potential participants (97.4% of all living, located) were contacted by telephone to request participation. An additional 93 (2.1% of all living, located) were located to an address, and were sent one or more letters, but could not be contacted by telephone[2]. A total of 3564 potential participants (84.1% of those who were contacted by telephone, 81.9% of all located, living) agreed on either a first or a second attempt. Of those located alive, 634 (14.6%) refused to participate in the study.

Forty-one living located potential participants (0.9%) were determined to be unable to fully participate and were consequently not included in the study regardless of willingness to participate. Twenty-five were reported by others (parents, guardians or caregivers) to be incapable of participating due to mental or physical/medical disability. In these cases, contact with the person directly was not possible and could not be considered a refusal. Of the remaining 16, six were incarcerated out of state for the duration of the study; three were not opposed to participating, but were living outside of the U.S. and had no plans to return to the U.S. during the study; the remaining seven were either adopted, and/or did not have sufficient information regarding residence history of the birth mother or their early childhood to accurately assess residence/dose, and therefore would not have been evaluable (see section IV.B above for definition of evaluable participant).

[2]Either no phone number was available or multiple attempts to reach by phone resulted in no contact.

Figure V.C-13. Final Agreement to Participate for the Entire Study (N = 4350)

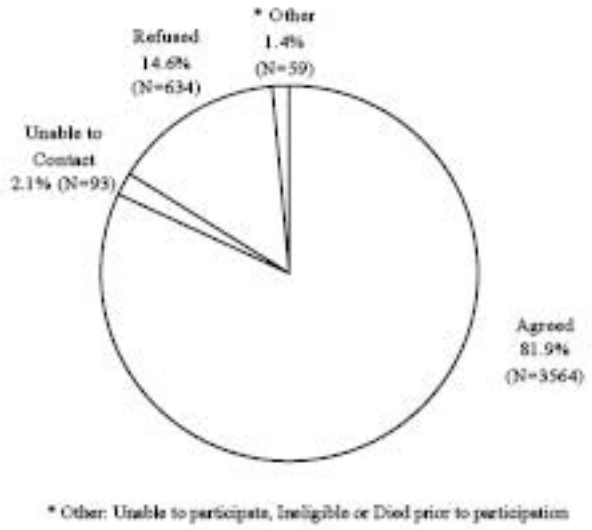
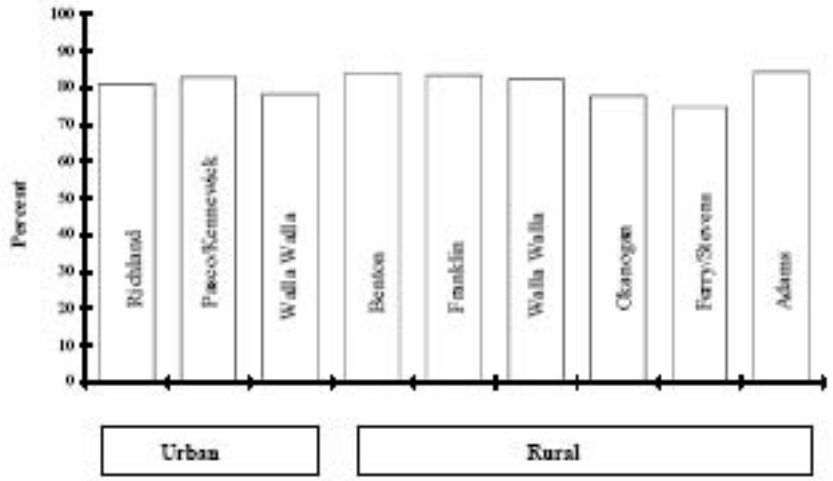


Table V.C-7. Summary of Agreement or Refusal for the Entire Study (N=4350)

Contact Status	No.	% of Contacted by Phone	% of Letter Sent	% of Total
Letter Sent	4329	--	100.0	99.5
Unable to contact	90	--	2.1	2.1
Contacted by phone	4239	100.0	97.9	97.4
Agreed, final	3564	84.1	82.3	81.9
- on first attempt	3446	81.3	79.6	79.2
- on second attempt	118	2.8	2.7	2.7
Refused, final	634	15.0	14.6	14.6
Unable to participate	41	1.0	0.9	0.9
Died prior to participation	16	--	--	0.4
Ineligible	2	--	--	0.0
Located with no contact	3	--	--	0.1

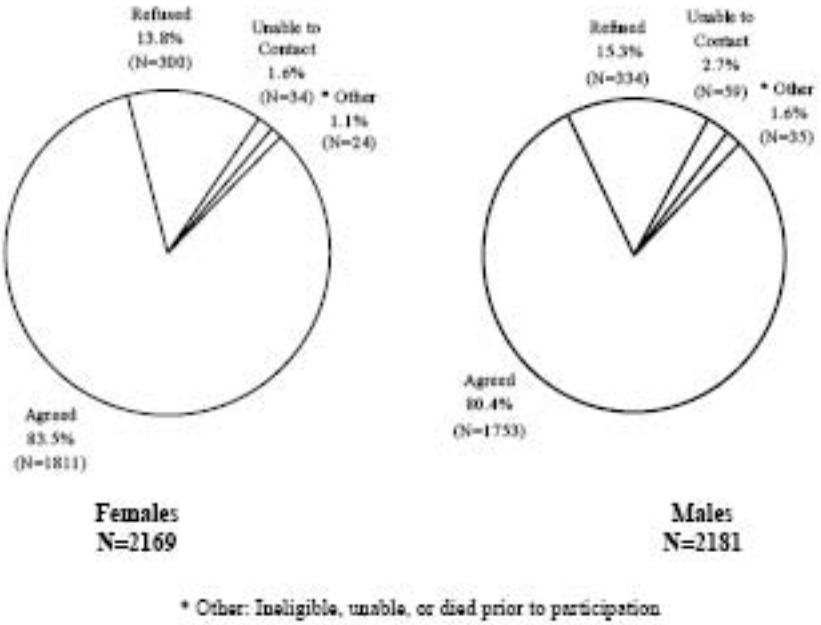
Agreement to participate is shown by geostrata in Figure V.C-14. While those born in Ferry and Stevens Counties had the lowest agreement rate at 74.5%, willingness to participate did not otherwise differ substantially by geographic region of birth. Agreement rates from all other geographic strata ranged from 77.7-84.3%.

Figure V.C-14. Final Agreement to Participate for the Entire Study, by Geostratum (N=4350)



Agreement to participate is shown by sex for the entire study in Figure V.C-15. Women were slightly more likely to agree than men, 83.5% and 80.4% respectively.

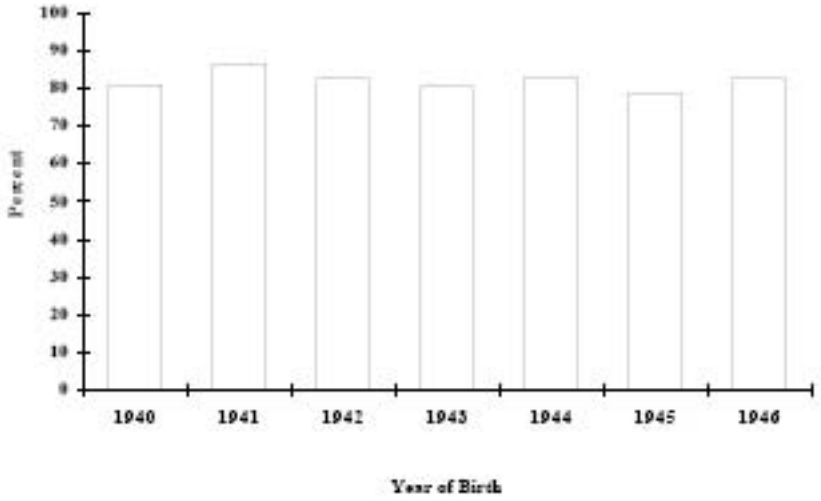
Figure V.C-15. Final Agreement to Participate for the Entire Study, by Sex (N = 4350)



* Other: Ineligible, unable, or died prior to participation

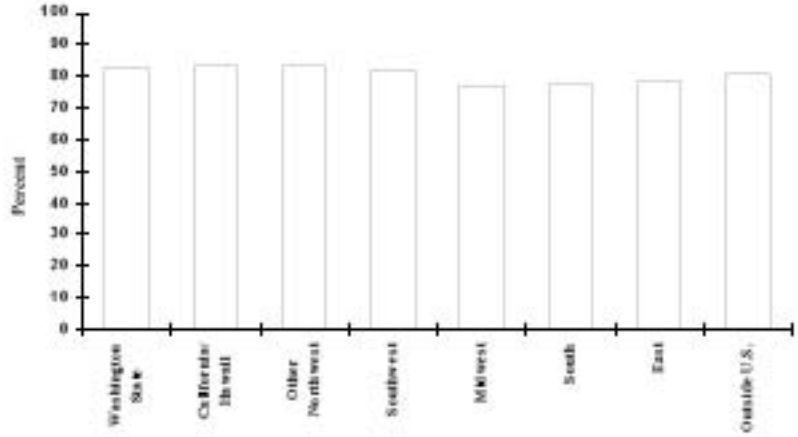
Willingness to participate did not vary appreciably by birth year, as shown in Figure V.C-16. Agreement rates range from 78.8% to 86.6% for the seven years of birth (1940-1946), with no apparent pattern.

Figure V.C-16. Final Agreement to Participate for the Entire Study, by Year of Birth (N=4350)



Agreement to participate by area of current residence is shown in Figure V.C-17. A slight variation was evident by region of the country. Agreement rates in the Midwest, Southern and Eastern portions of the US ranged from 77.0-78.4%, whereas in the western U.S. they ranged from 82.1-83.1%. Those living outside the U.S. had an agreement rate of 80.6%.

Figure V.C-17. Final Agreement to Participate for the Entire Study, by Geographic Region of Current Residence (N=4350)



The Regions in Figure V.C-17 were defined as follows:

Washington State	
Cal/Hawaii:	- California, Hawaii
Other Northwest:	- Alaska, Idaho, Montana, Oregon, and Wyoming
Southwest:	- Arizona, Colorado, Nevada, New Mexico, Texas, Utah
Midwest:	- Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin
South:	- Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee
East:	- Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Washington D.C., West Virginia

C.3.d.1. Agreement on First Attempt vs. Second Attempt (conversions)

Of those who "ever agreed" (3862), 95.9% (3704) agreed on the first attempt while 4.4% (172) agreed on the second attempt refusal conversion. Of all potential participants who "ever agreed," those agreeing on the second attempt were more likely to withdraw and/or never attend a clinic (39.5%), compared to those who agreed on the first attempt, but withdrew or never attended a clinic (9.6%). Nonetheless, it is still noteworthy that of the 172 potential participants whose initial refusal was converted to an agreement on a second attempt, 104 (60.5%) did eventually attend clinics, making up 3% of all participants attending clinics.

Table V.C-8 shows the reasons given for refusal or withdrawal, by geographic area of current residence. Overwhelmingly, "Not Interested" and "No Time" were the main reasons cited for non-participation, with 64.8% of all refusals falling into this category. The next highest category, at 7.6% (48 cohort members) was illness or impairment. In general, the reasons given did not vary significantly by area of current residence, although fewer Washington State residences cited unwillingness to travel as compared to those outside the state. Still, this reason accounted for only 30 (4.7%) refusals to participate.

Table V.C-8. Reasons for Refusal or Withdrawal for the Entire Study, by Geographic Area of Current Residence (N=634)

Area of Current Residence	Reason for Refusal or Withdrawal														
	Not Interested or No Time		Illness or Impairment		Unwilling to Travel		Opposed to Study		Legal or Insurance Concerns		No Thyroid Disease		Other*		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
All WA	216	66.1	21	6.4	3	0.9	17	5.2	5	1.5	2	0.6	63	19.3	327
Seattle	28	63.6	2	4.5	0	--	1	2.3	1	2.3	0	--	12	27.3	44
Everett	7	58.3	1	8.3	0	--	1	8.3	0	--	0	--	3	25.0	12
Tacoma	11	73.3	0	--	0	--	0	--	0	--	0	--	4	26.7	15
Olympia	10	66.7	2	13.3	1	6.7	0	--	0	--	0	--	2	13.3	15
SW WA	12	66.7	0	--	0	--	3	16.7	0	--	0	--	3	16.7	18
Wenatchee	19	79.2	3	12.5	0	--	0	--	0	--	0	--	2	8.3	24
Yakima	14	53.8	3	11.5	1	3.8	1	3.8	2	7.7	0	0	5	19.2	26
Spokane	39	69.6	3	5.4	0	0	4	7.1	0	--	1	1.8	9	16.1	56
Tri-Cities	75	64.7	7	6.0	1	0.9	7	6.0	2	1.7	1	0.9	23	19.8	116
SE WA	1	100	0	--	0	--	0	--	0	--	0	--	0	--	1
Other NW	51	57.3	9	10.1	5	5.6	2	2.2	2	2.2	2	2.2	18	20.2	89
CA/HI	35	64.8	8	14.8	4	7.4	2	3.7	1	1.9	0	--	4	7.4	54
Southwest	30	69.8	5	11.6	2	4.7	3	7.0	0	--	0	--	3	7.0	43
Midwest	34	66.7	4	7.8	7	13.7	0	--	0	--	1	2.0	5	9.8	51
South	26	63.4	0	--	8	19.5	0	--	0	--	0	--	7	17.1	41
East	18	69.2	1	3.8	0	--	1	3.8	0	--	1	3.8	5	19.2	26
Other	1	33.3	0	--	1	33.3	0	--	0	--	0	--	1	33.3	3
Total	411	64.8	48	7.6	30	4.7	25	3.9	8	1.3	6	0.9	106	16.7	634

* Other: Includes family problems, personal reasons, distrust, lack of personal benefit, scheduling problems, refusal by a household member on the potential participant's behalf, and no reason given.

C.3.d.2. Refusals

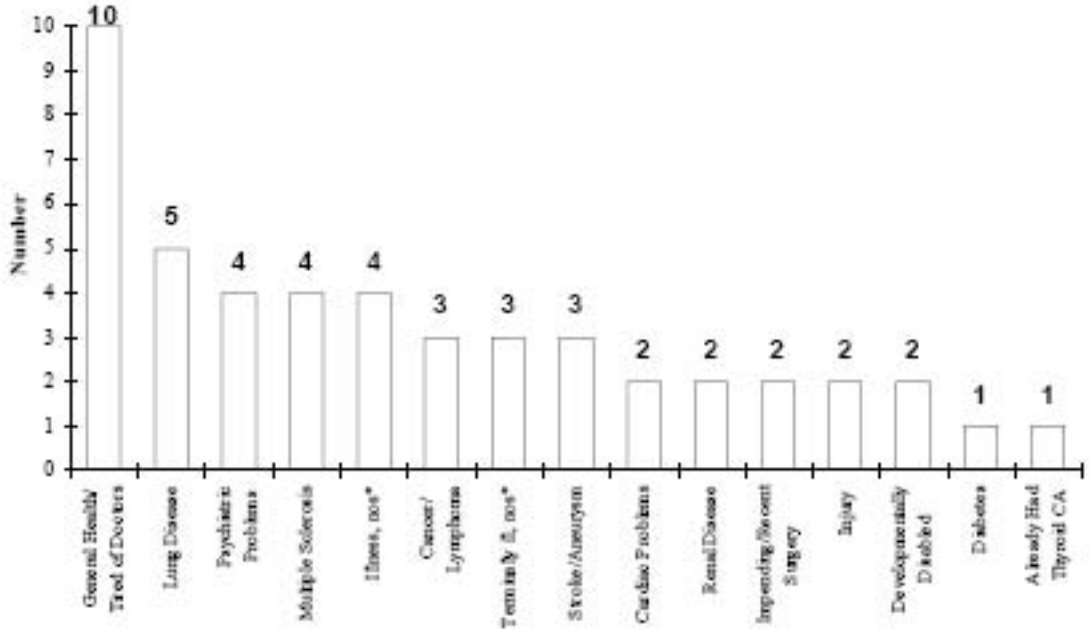
Among the final refusals (those either not recontacted or if recontacted, not converted to agreement), overwhelmingly, "not interested" and/or "no time" were the reasons given for most refusals, making up 31.9% and 33.0%, respectively. Other frequently cited reasons were "illness" (5.5%), "unwilling to travel" (4.7%), and "opposed to study" (3.9%). Particular efforts were made to accommodate potential participants who cited illness as a reason for being unable to participate, including repeated contacts, covering the cost of travel companion, special food, lodging and local travel accommodations. Nineteen (3.0%) responses indicated that a person other than the potential participant refused for the potential participant or discouraged them from participating. These were often spouses who were opposed to participation or who claimed to be responding on their spouse's behalf. While every effort was made to talk to the potential participant directly, the policy was not to pursue cases in which a family member would refuse for or not allow contact with the potential participant. In such cases, no further contact was attempted. This situation was thus considered a refusal to participate.

In eleven cases, the reason for non-participation was that the potential participant and Scheduler could not agree upon an acceptable clinic appointment. In most cases, this was simply due to the potential participant's extremely busy schedule at work and/or home, which precluded a genuinely interested participant from attending the clinic.

For those who refused or withdrew from the study due to illness, or were judged unable to participate due to impairment, the reason for their non-participation was recorded at the time of the refusal or withdrawal. The type of illness or impairment was recorded in the Recruiter's notes on the Refusal

Assessment Form. Figure V.C-18 summarizes the types of illnesses and impairments that precluded participation in the study. For those potential participants in the "Other" category reasons ranged from wanting the study to pay for their spouse to travel to the clinic with them for a vacation, to feeling that participation in a study with a politically controversial topic would conflict with their religious beliefs. In no case was current thyroid disease given as a reason for non-participation, however, one potential participant did state he/she did not wish to participate because he/she had already undergone a thyroidectomy for cancer and did not wish to have additional studies for this condition.

Figure V.C-18. Type of Illness/Impairment Precluding Participation for the Entire Study (N=48)



*nos = not otherwise specified

C.3.d.3. Success in Converting Refusals/Withdrawals by Reason for Refusal

With the exception of those who cited illness or gave no reason, there was relatively little variation in the success rate for converting initial refusals (shown in Table V.C-9, below). Success rates were higher for those who gave a reason of "no time" or "not interested" initially, and were highest for those who cited illness as the reason for initial refusal. The percent of conversions of those contacted a second time ranged from 0% for those reporting impairment as the reason for their refusal to 81% who refused for "other reasons".

Table V.C-9. Conversion to Agreement to Participate by Reason for Refusal for the Entire Study

		Recontacted		Converted to Agreement		
Reasons Refused	Total	No.	%	No.	% of Recontacted	% of Total
No time	250	147	58.8	41	27.9	16.4
Not interested	242	156	64.5	40	25.6	16.5
Illness	40	9	22.5	5	55.6	12.5
No reason given	34	9	26.5	4	44.4	11.8
Unwilling to travel	33	14	42.4	3	21.4	9.1
Opposed to study	29	15	51.7	4	26.7	13.8
Other person refused	22	12	54.6	3	25.0	13.6
Family problems	15	8	53.3	3	37.5	20.0
Impaired	13	3	23.1	0	0.0	0.0
Scheduling problems	11	0	0.0	0	0.0	0.0
No thyroid disease	6	2	33.3	0	0.0	0.0
Distrustful/suspicious	6	3	50.0	0	0.0	0.0
Advice of attorney	5	4	80.0	1	25.0	20.0
Insurance concerns	5	3	60.0	1	33.3	20.0
No personal benefit	5	0	0.0	0	0.0	0.0
Personal reasons	5	1	20.0	0	0.0	0.0
CATI upset respondent	3	2	66.7	0	0.0	0.0
Other reason	28	16	57.1	13	81.2	46.4
Total	752	404	53.7	118	29.2	15.7

* All who "ever agreed" on second attempt, including those who later withdrew

C.3.d.4. Success in Converting Refusals/Withdrawals by "Strength" of Refusal

It should be noted that whether or not a potential participant was re-contacted for a second attempt at recruitment was based on the Recruiter's or Participation Coordinator's discretion, potentially producing an inherently biased, "pre-selected" group of participants who were contacted for a second attempt. This may, in turn, affect the ability to accurately compare success in converting refusals by strength of refusal or other variables. With this in mind, it is still of interest to consider the success rates of refusal conversion by strength of initial refusal and by reason for refusal.

Fifty-six percent (245) of those classified as "firm" in their refusal on first attempt were re-contacted, while 60.9% (143) of those whose refusal was categorized as "mild" were contacted for a second attempt. Of those whose response was considered "hostile" on the first attempt, a total of 16 (20%) were designated for re-contact. These few potential participants were felt eligible for re-contact based on the point at which the refusal occurred (generally in the first seconds of the recruitment call).

Success in converting refusals to agreement to participate, when potential participants were re-contacted for a second attempt, did appear related to the strength of the initial refusal or withdrawal (classified by the Recruiter as mild, firm, or hostile). When contacted for a second attempt, 36.4% of participants whose refusal was categorized as "mild" agreed on a second attempt. In comparison, 24.5% of the participants who had been reported as "firm" in their refusal on the first attempt agreed on the second attempt. Interestingly, of those judged "hostile" on initial contact who were re-contacted, 37.5% agreed on the second attempt. This was, however, a small and highly select group, which would not represent "hostile" refusers as a whole.

The variation in success rates for conversion of refusals when comparing all potential participants (whether re-contacted or not) by strength of refusal was similar between the "mild" and "firm" refusals, 22.1% and 13.7%, respectively. Table V.C-10 shows conversion to agreement by strength of refusal.

Table V.C-10. Conversion to Agreement to Participate by Strength of Refusal for the Entire Study

Strength of Refusal	No.	Re-contacted	%	Converted	% Converted of Re-contacted	% Converted of Total Refused
Mild	235	143	60.9	52	36.4	22.1
Firm	437	245	56.1	60	24.5	13.7
Hostile	80	16	20.0	6	37.5	7.5
Total	752	404	53.7	118	29.2	15.7

While the attempts to convert initial refusals or withdrawals appear to be more successful when re-contacting those whose refusals were classified as mild, with 13.7% of all "firm" refusals/withdrawals agreeing to participate on the second attempt, it also seemed worthwhile to attempt to convert most potential participants regardless of perceived strength of first refusal (with the exception of truly hostile potential participants who were generally not re-contacted).

C.3.e. Conclusions

Efforts to recruit participants for this study were successful and met or exceeded initial expectations. Although participation required a substantial effort on the part of the participant and his/her family, these rates of success indicate a substantial degree of general willingness of those selected to participate in this study.

An important part of this success can be attributed to highly trained recruiting staff who was able to respond appropriately to potential participants' concerns. The approach of sending detailed study information prior to contacting potential participants seemed to work well for the purposes of recruiting. In addition, re-contacting many potential participants who refused on the first attempt (or withdrew), resulted in substantial refusal conversions and a 3% increase in those ultimately attending a clinic.

D. Computer Assisted Telephone Interview

D.1. Background

Two basic approaches were considered for collecting information about study participants' early years of life: 1) a personal interview with one respondent and other members of the family present; and 2) a telephone interview with a respondent and other family members connected by a conference call. The approach of conducting a personal interview was deemed not to be feasible due to the logistical complexities of organizing such interviews all over the country and the very high costs that would be associated with such a process. A decision was made to proceed with the development of a Computer Assisted Telephone Interview (CATI). The idea of involving more than one person was later incorporated, to a limited degree, when special circumstances dictated that an additional person (or persons) would enhance the recall of specific information (e.g., cow feeding patterns).

D.1.a. Objectives of the Interview

The primary objective of the CATI was to collect information that would be used as input for calculating a radiation dose to the thyroid gland from Hanford's ^{131}I for each study participant, as well as information about other radiation exposures and diagnoses of thyroid disease experienced by the participant. Secondary objectives of the CATI component of the study were to: 1) interview a person knowledgeable about each participant's early life (e.g., someone who could answer questions about the whereabouts, circumstances, and habits that an individual could not be expected to know about his/her very early years); and 2) assure that the accuracy and integrity of the data collected were of acceptable quality.

D.1.b. Historical Perspective and Special Challenges

Prior to the time that the HTDS began developing a CATI for dose determination purposes, the CATI technique had been used extensively for several years by many organizations, primarily to conduct telephone surveys for health and opinion research. A CATI is conducted by an interviewer who reads the survey text and questions from a computer screen. As the respondent provides each answer, the interviewer enters the response into the computer, and the response immediately becomes part of the permanent database. The computer program is designed to show the next question on the screen that should be asked, based on the previous answer(s).

Surveys conducted with CATI are generally quite straightforward, and they are usually structured in such a way that the questions are formatted for multiple choice, true/false - agree/disagree, and short answer responses. The total interview time is seldom greater than twenty minutes, and the respondent does not prepare in advance for the interview. CATI is often used in conjunction with "cold calling" to identify respondents willing to spend a few minutes on the telephone participating in a survey.

In the initial stages of planning the HTDS CATI, it became apparent that the interview would be far more complex than is typical of the CATI format. It appeared that the "state of the art" for CATI methodology did not incorporate many of the key features that would be required for the HTDS CATI. Several characteristics of the HTDS posed special challenges to developing a workable CATI.

First, much of the information required pertains to events that happened between forty and fifty years before the interview. Furthermore, much of the information in the interview could be considered rather mundane in that the questions would need to refer to events and circumstances of daily life. Clearly, asking people to recall such detailed information from so long ago would present very special challenges.

Second, a large volume of information would need to be collected during the interview. It would be necessary to develop a structure that would organize the various types of data collected, while

accommodating a wide range of life circumstances among the study participants. For example, some participants were born in the study area while their parents resided there only temporarily, perhaps for only a few weeks, before moving out of the Northwest. Such an interview would yield a relatively small amount of data. Other participants were born and lived their entire lives in the area, perhaps at multiple residences. An interview about such an individual could produce a much larger amount of data. It would be important to have computer software that could adequately adjust to the very different circumstances that would likely arise, and the variations in the amount of data collected. Third, and related, it would be critically important that the system be capable of managing complex skip patterns, and allow for on-line consistency checks and the ability to correct entries on-line.

D.2. Content and Design of the CATI

The plan for CATI described in the HTDS Protocol provided the rationale for the content of the interview and identified its components. It was designed to collect information from the early years of the participants' lives, including time *in utero,* from 1944 to 1957. The period of greatest interest, with regard to exposure to radioactive iodine, was each participant's early childhood. The interview was "location-driven" so that the information collected was specific to locations and periods of time directly relevant to the radiation releases from Hanford.

The following topic areas were included in the CATI: 1) a residential history of the participant from birth through 1957, and for the mother while pregnant with and breastfeeding the participant; 2) sources of milk consumed by the participant from birth through 1957, and for the participant's mother while pregnant and breastfeeding (including commercial milk producers and private sources, for both cow's and goat's milk; 3) milk consumption patterns for the participant from birth through 1957, and for the mother during pregnancy and breastfeeding; 4) other patterns of food consumption, including green and leafy vegetables, fresh fruit and free-range chicken eggs, for the participant from birth through 1957, and for the mother while pregnant and breastfeeding. In addition, medical history information was obtained for both the mother and the participant, including the following: 1) thyroid diseases and selected other medical conditions diagnosed and treated in the participant; 2) history of radiation exposures, either diagnostic or therapeutic, for the participant, and for the mother during pregnancy and breastfeeding. The name of the treating physician for these conditions and treatments was obtained when possible.

The CATI was developed in cooperation with a number of individuals and groups, including the Technical Steering Panel of the Hanford Environmental Dose Reconstruction Project and Battelle Pacific Northwest Laboratories, staff at the CDC, scientists who had conducted similar studies (e.g., Dr. Lynn Lyon at the University of Utah), and experts in survey and cognitive research.

After extensive investigation of available software options, the INGRES software package was selected as the basis for developing the CATI. INGRES provided a relational database structure, which was judged to be essential for the type of system envisioned, and contained many of the technical features needed to accommodate a complex interview with on-line quality control.

The CATI was administered to the participant's mother, or other person knowledgeable about the participant's early years, by specially trained interviewers. The interview was recorded on audiotape with the respondent's permission, so that a permanent record, independent of the computer system, would be created. The recording could be used for back-up to the computer system, for training and quality control monitoring of interviewers, and for clarification of information provided during the interview.

D.2.a. Development of a Cognitive Approach to Enhance Long-term Recall

From the initial stage of questionnaire development it was apparent that making the interview successful would depend largely on the ability of respondents to accurately report detailed information

about their child (or sibling) from very long ago. In July 1990 a workshop was held to consider how the questionnaire and the process of conducting the CATI interview could be modified to include as many characteristics of a cognitive interview as possible. Participants in the workshop included Dr. Donald Dillman, a sociologist and leading national authority on survey research from the Washington State University at Pullman; Dr. Ronald Fisher, a cognitive psychologist from Florida International University; and Dr. David Price, an agricultural economist and member of the Hanford Environmental Dose Reconstruction Project Technical Steering Panel from Washington State University, the four HTDS investigators, and key HTDS staff (Project Manager, Programmer, Field Operations Supervisor). Dr. Dillman's expertise in interview data collection has been utilized by the U.S. Department of the Census, while Dr. Fisher's work has been used extensively to assist in both criminal investigation and investigations of food-borne illness.

The cognitive interview is a technique developed to enhance recall. It is based on principles of cognition and memory retrieval theory. In the cognitive interview, it is important to mentally take the respondent back to the time period in question, and have them remember as much about that time as possible. As more memories of the time in question are recalled by the respondent, the likelihood of remembering answers to specific questions increases. Thus, for an interview regarding food consumption patterns such as the HTDS CATI, one would want to guide the respondent to remember not only major events or favorite songs of the time, but what the kitchen where the food was prepared looked like, and where food was purchased. These principals of the cognitive interview, with extensive preparation by the respondent, differ greatly from the standard epidemiologic interview. In most epidemiologic studies, great care is taken to ensure that the respondent does not prepare in advance to answer questions. Such preparation, it is felt, could produce bias in that those who are ill may be more likely to prepare and report exposure than those who are not. However, these studies also generally do not ask such specific questions about daily life events so many years after the fact.

D.2.b. Development and Testing of the CATI

During the spring of 1991 the first field testing of a paper version of the questionnaire took place in the Tri-Cities area. Individuals who had offered to help the study in some way were asked to participate in the testing. Three interviews were conducted with people in their homes. These individuals closely fit the profile of a CATI respondent. Generally, they were in the same age range as the parents of study participants, and they had children who were born during nearly the same years as study participants. Care was taken not to include individuals who could possibly be asked later to participate in the actual study.

Major conclusions drawn from this field test included the following: 1) it was too difficult for respondents to look at maps and determine the exact locations of residences; 2) the memory prompts previously developed were helpful, but needed to be expanded to encourage advance preparation by the respondent; 3) asking respondents to identify all residences during the interview without preparing beforehand was too difficult; and 4) giving the respondent the opportunity to prepare ahead of time for the interview was very important, and would be a major determinant in obtaining a successful interview.

During the early summer of 1992, Dr. John Tarnai, a sociologist from Washington State University and colleague of Dr. Don Dillman, began working with the HTDS staff on expanding and refining the memory materials that would be provided to respondents in preparation for the interview. As a result of the field testing concluded in 1991, it was decided to ask respondents to provide a written residence history to be mailed to the study office prior to conducting the interview. One goal of the memory materials was to encourage recall for completion of the residence history by providing information about events that happened during each year of interest. World, national, and local events, as well as popular songs, movies, and trends from each year were included to help provide a frame of reference that would help direct memory to many years ago.

Additional memory materials were developed to help the respondent prepare for answering the interview questions. Background information was provided to encourage memory about specific topics. For example, the dates of VE Day and the death of President Roosevelt were provided as general reference dates, while the beginning of war rationing and the Tri-Cites Memorial Day flood of 1948 were added to focus on local events which might have impacted food consumption practices. The memory materials were organized into a booklet that was to be sent with the residence history questionnaire. In addition, the text of the interview was refined to include references to specific parts of the memory materials at key points during the interview.

A second and more extensive field test was conducted during July and August of 1992. Telephone interviews were conducted with parents, friends, relatives of HTDS and other FHCRC staff members, and a few individuals recruited from local senior citizens centers. All respondents were similar in age to the parents of study participants. Precautions were taken to ensure that none of the individuals involved could later be asked to participate in the study. Fifteen individuals participated as respondents in this effort.

This round of field testing consisted of two parts. Interviews were completed with about half the individuals, and they were then asked to provide feedback about the interview experience. The primary finding was that the volume of materials provided for memory recall purposes was overwhelming. As a result, the materials were divided into two parts. The first booklet, titled the Calendar of Events (Appendix 7), would accompany the Residence History Questionnaire (Appendix 8) that respondents would complete and mail back prior to the interview. The second, titled the Interview Booklet (Appendix 9), was designed to contain information that would help prepare for answering the interview questions. The Interview Booklet was to be mailed a few days after the Calendar of Events and Residence History Questionnaire were sent.

The revised materials, sent out in two separate mailings, were used during the second part of field testing. These later interviews confirmed that dividing the materials was easier for the respondents, as the volume of information was not so intimidating. In response to comments from the second group that it was difficult to foresee what the questions in the interview would be like, a sheet of sample questions was developed. An additional page of materials entitled "Meet the Johnsons," presented a profile of a typical family, then gave examples of questions from the interview with the appropriate responses, based on information provided in the profile. This sheet was enclosed with the Interview Booklet, and is included here as Appendix 10.

Additional smaller refinements to the questionnaire text were made during the early fall of 1992, as a result of the CATI training and practice interviews (Appendix 11).

D.2.c. Final Process and Procedures

D.2.c.1. Conducting the Interview

Each participant recruited for the study was asked to identify a respondent for the CATI as described in section V.C.2.b above. This person was to be knowledgeable regarding the participant's early life and eating habits, able to perform the required preparation for the interview, and able to respond to the questions over the phone during a conversation that could be over an hour in length.

Once the respondent was identified, a letter was sent informing her or him that the participant had asked that they complete this portion of the study. This letter was followed by a phone call from the Interviewer to explain the process and obtain consent to do the CATI. If the respondent declined to do the interview, the participant was recontacted to determine if another respondent was available. If the respondent consented to the interview, the Residence History Questionnaire and Calendar of Events were sent to them to complete. The Residence History Questionnaire was to be sent back to the Interviewer, and once received, the Interviewer called the respondent to review the information and schedule the actual

interview. With the respondent's consent, interviews were recorded on audiotape for quality control and interviewer training purposes.

Once the interview was completed, the Interviewer updated the tracking system, so the participant could be scheduled for a clinic appointment. A thank-you letter was sent to each respondent in appreciation of his or her participation in the study.

D.2.c.2. Quality Control

Quality control for the CATI was first addressed in the thorough training given to each interviewer prior to performing actual interviews. Each interviewer was provided extensive training on both the interview instrument as well as the computer system required to administer the CATI. Over the course of the study, seven interviewers were trained to conduct the CATI. Each interviewer received written materials including a flow diagram of the entire interview, a question-by-question training manual, and a manual covering interviewing techniques such as appropriate probing and responses to respondent questions. In addition, they received documentation of the CATI program, special training on making data corrections during the interview (when respondents changed their minds regarding a previous answer), and a procedure manual outlining the CATI process from initial contact to completion of the interview.

When the study first began, the original three interviewers traveled to Washington State University in Pullman for training in the cognitive interview technique. Two additional interviewers underwent this training later in the study, while the final two interviewers hired received this portion of the training from experienced HTDS interviewers.

Interviewers continued their training by conducting the interview with HTDS staff, family and friends. This was followed by practice interviews with volunteers (often the parents of HTDS staff members) who had children in the age range of study participants. Tapes of these "practice" interviews were reviewed with the CATI Supervisor and experienced interviewers for feedback on technique and accuracy. Later in the study, new interviewers began their training by listening to previous interviews with an experienced interviewer.

Throughout the study, the CATI supervisor listened to tapes of the interviews as part of the quality control plan. Checks of the data entered during the interview were compared to the answers given on the tape. Any necessary data corrections were performed by the systems analyst/programmer. Feedback on any errors found was given to individual interviewers by the CATI Supervisor. In addition, early in the study, tapes were copied and forwarded to Dr. John Tarnai and Ms. Ellen Lammiman of Washington State University, Pullman. These recordings were reviewed for interviewer technique in assisting recall of participants, appropriate probing questions, and consistency. Feedback from Dr. Tarnai and Ms. Lammiman was forwarded to the interviewers as part of the ongoing assessment of their work. Sampling of tapes was performed on a random basis for two interviews per week during the first six months of the study. Additional tapes were monitored following the training of new interviewers, or when specific issues were found. Random checks continued throughout the study at a rate of approximately one interview per week.

Quality assessment of the respondent's ability to answer the interview questions was also performed. Following each section of the interview, interviewers recorded their assessment of how reliable the responses were for those questions using the categories of High, Generally Reliable, Questionable, or Unreliable. These assessments were based on whether the respondent seemed fairly certain of the responses, appeared to be guessing or asking the interviewer for help in making the "correct" response, and whether the responses were consistent or contradictory. At the end of the interview, the interviewer also recorded her or his overall assessment of the reliability of the responses, and of the respondent's level of cooperation (Very Good, Good Fair, or Poor).

D.3. Outcome and Results

D.3.a. Pilot Study Results

CATIs were completed for 797 (85.1%) of the 937 participants in the Pilot Study Sample who identified a CATI respondent. Of the 1063 Pilot Study participants who completed the clinic, 756 (71.1%) had a complete CATI interview. Forty-one participants withdrew from participation after the CATI was completed. In 14 instances, CATI Interviewers deemed the quality of the data provided by respondents too poor to be considered reliable. Expanded interviews were performed at the clinic for these participants.

D.3.b. Transition Sample Results

Of the 536 participants in the Transition Sample who identified a CATI respondent, interviews were completed for 458 (85.4%). Of the 664 Transition Sample participants who completed the clinic, 429 (64.6%) had a CATI. Twenty-nine participants withdrew from the study after a CATI was completed. In two instances, CATI Interviewers determined that the quality of the data provided by respondents was too poor to be considered reliable. Expanded interviews were performed at the clinic for these participants.

D.3.c. Results for the Full Study Sample

CATIs were completed for 1011 (81.6%) of the 1239 participants in the Full Study Sample who identified a CATI respondent. Of the 1720 Full Study Sample participants who completed the clinic, 948 (55.1%) had a CATI. Sixty-three participants withdrew from the study after a CATI was completed. In 13 instances, CATI Interviewers determined that the quality of the data provided by respondents was too poor to be considered reliable. Expanded interviews were performed at the clinic for these participants.

D.3.d. Overall Results for the Entire Study

Of the 2712 participants who identified a CATI respondent in the entire study, interviews were completed for 2266 (83.6%). Of the 3447 eligible participants who completed the clinic, 2133 (61.9%) had a CATI. One hundred-thirty-three participants withdrew from the study after a CATI was completed. In 29 of the 2133 instances, CATI Interviewers determined the quality of the data provided by respondents was too poor to be considered reliable. Expanded interviews were performed at the clinic for these participants.

D.3.e. Conclusions

The percentage of CATIs completed for participants declined with each successive phase of the study. This can probably be attributed to the fact that respondents were somewhat older as the study progressed, especially following the Full Study Sample. Participants born in 1940 and 1941 were included at this time, and this small difference in birth years may have contributed to the decrease in the overall percentage of CATIs completed. Table V.D-1 shows the number of CATIs completed by year of participant's birth.

Table V.D-1. Final Outcome of CATI by Participant's Year of Birth for the Entire Study (N =2712*)

Year of Birth	Respondent Identified	CATI Completed* No.	CATI Completed* % of those w/Respondent Identified	CATI Completed for those Attending a Clinic	% of those Attending a Clinic with CATI
1940	164	135	82.3	128	52.0
1941	170	136	80.0	129	45.3
1942	366	317	86.6	299	63.2
1943	438	348	79.5	326	58.2
1944	742	608	81.9	569	62.7
1945	504	436	86.5	412	67.4
1946	328	286	87.2	270	74.0

* Includes all CATIs completed, whether acceptable for dose determination or not.

D.3.e.1. Quality of the Data

Overall data quality was very high as reported by the interviewers. Tables V.D-2 through V.D-4 show the assessment of data reliability as reported by the CATI interviewers. Responses were judged to be of high quality or generally reliable for most interviews for most sections. Responses in the section related to the participant's milk and dietary consumption history were judged by the interviewers to be questionable in approximately 9% of the interviews. Not surprisingly, the main reason cited for questionable or unreliable responses was unclear memory. The interviewer judged the respondent's cooperation to be good or very good in over 94% of the interviews.

Table V.D-2. Interviewer's Overall Assessment of Reliability of Responses to CATI (CATIs Used for Dose Estimation Only) for the Entire Study (N=2123)

	Overall		Milk Source Data		Mother's Milk Consumption and Dietary Data		Participant's Milk Consumption and Dietary Data		Mother's Medical History		Participant's Medical History	
Response Quality	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
High	410	19.3	387	18.2	377	17.8	297	14.0	1178	55.5	951	44.8
Generally reliable	1523	71.7	1570	74.0	1552	73.1	1483	69.9	910	42.9	1118	52.7
Questionable	170	8.0	39	1.8	53	2.5	193	9.1	23	1.1	44	2.1
Unreliable	11	0.5	0	0	1	0	10	0.5	3	0.1	4	0.2
Unknown	9	0.4	127	6.0	140	6.6	140	6.6	9	0.4	6	0.3

Table V.D-3. Main Reasons for Unreliable or Questionable Responses to CATI (CATIs Used for Dose Estimation Only) for the Entire Study (N=2123)

	Overall		Milk Source Data		Mother's Milk Consumption		Participant's Milk Consumption and Dietary Data		Mother's Medical History		Participant's Medical History	
Response Quality	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Unclear memory of events	136	6.4	34	1.6	41	1.9	141	6.6	21	1.0	35	1.6
Uncertain understanding of questions	9	0.4	1	0	2	0.1	17	0.8	0	0	1	0
Hurried responses	8	0.4	1	0	2	0.1	11	0.5	0	0	1	0
Other	28	1.3	3	0.1	8	0.4	33	1.6	5	0.2	9	0.4
Don't know	0	0	0	0	1	0	1	0	0	0	2	0.1
Not applicable*	1942	91.5	2084	98.2	2069	97.5	1920	90.4	2097	98.8	2075	97.7

* Response quality High, Generally Reliable or Unknown

Table V.D-4. CATI Interviewer's Assessment of Respondent's Cooperation (CATIs Used for Dose Estimation Only) for the Entire Study (N = 2123)

Respondent's Cooperation	No.	%
Very good	1511	71.2
Good	496	23.4
Fair	99	4.7
Poor	8	0.4
Not answered	9	0.4

It was anticipated from the beginning of the study that participants' mothers would be the most reliable respondents for the majority of the interview questions, as mothers would be most familiar with the participant's dietary habits and medical histories. This was generally the case. Table V.D-5 shows the relationship of the respondent to the study participant, while Table V.D-6 shows the quality of the CATI data by the respondent's relationship to the participant.

Table V.D-5. Relationship of CATI Respondent to Participant for the Entire Study

	All Persons Who Agreed To Participate		Living Evaluable Participants			
	All Interviews (N=2268)		All Interviews (N=2133)		Interviews Used as Source of Dosimetry Data (N=2123)	
Relationship to Respondent	No.	%	No.	%	No.	%
Birth mother	1674	73.8	1577	73.9	1568	73.9
Adopted mother	8	0.4	6	0.3	6	0.3
Father	167	7.4	158	7.4	158	7.4
Sister	289	12.7	270	12.7	270	12.7
Brother	89	3.9	82	3.8	81	3.8
Aunt	29	1.3	28	1.3	28	1.3
Uncle	4	0.2	4	0.2	4	0.2
Other relative	3	0.1	3	0.1	3	0.1
Family friend	5	0.2	5	0.2	5	0.2

Table V.D-6. Quality of CATI Data by Respondent's Relationship to Participant for the Entire Study (N =2268)

Overall Response Quality	Birth Mother		Adopted Mother		Father		Older Sister		Older Brother		Other Family Member		Family Friend	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
High	328	19.6	0	0	28	16.8	59	20.4	23	25.8	1	2.8	1	20.0
Generally reliable	1203	71.9	7	87.5	121	72.5	208	72.0	54	60.7	23	63.9	1	20.0
Questionable	125	7.5	1	12.5	14	8.4	18	6.2	12	13.5	12	33.3	3	60.0
Unreliable	7	0.4	0	0.0	3	1.8	4	1.4	0	0.0	0	0.0	0	0.0
Unknown	11	0.7	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0	0	0.0
Total	1674		8		167		289		89		36		5	

D.4. Attempts to Administer the CATI to Respondents for Deceased Potential Participants

D.4.a. Development of a Revised CATI for Deceased Potential Participants

The HTDS Protocol stated that CATIs would be conducted for deceased potential participants, using the CATI respondent as a surrogate for the potential participants in collecting information contained in the In-Person Interview as well. A separate CATI instrument was developed for this purpose in the late summer of 1994. The questionnaire was an expansion of the original CATI, adding questions that were part of the In-Person Interview administered to living participants. These included questions about occupational history, smoking history, and demographics. It was recognized that, depending on the age of the potential participant at death, some questions would not be pertinent. Only those germane to the participant's life circumstances would be asked during the interview.

Special memory materials and interview preparation materials were developed for use with the revised CATI for deceased potential participants. Although similar to those for the interviews conducted for living participants, there were some differences in content: 1) the residence history information was collected from birth to death instead of through 1957 only; 2) a cause of death information questionnaire was added for the respondent to complete; and 3) sections about occupational history and smoking history were added to the Interview Booklet.

D.4.b. Conducting a CATI for Deceased Potential Participants

Thirty-three potential participants known to be deceased were selected from HTDS tracing records during the fall of 1994 to test the revised CATI process and instruments. Those selected included a large number of potential participants who died in infancy. The objective was to select cases for whom the interview would be comparatively uncomplicated. Letters of approach were sent to the respondents, and recruiting of the respondents was begun after about one week, as with living study participants. The CATI Interviewers found that the respondents had difficulties discussing the deceased potential participants and their lives.

The overall refusal rate among respondents for deceased potential participants was about 55% (18 of 33) at the end of this short pilot project. Although some respondents initially agreed to participate, as the process unfolded they found they could not proceed. They reported that the experience was just too painful for them to continue. Interviews were eventually completed for 15 of the 33 (45%) deceased potential participants.

Based on this pilot experience, it was decided that pursuing such an approach would be difficult for respondents and staff, and would not be likely to produce data of sufficient quality to be useful in estimating doses for deceased potential participants. Thus, in March of 1995, the decision was made not to attempt a CATI interview for deceased potential participants. The reasons for this decision were presented to the CDC and the HTDS Advisory Committee, who agreed that further attempts to perform CATIs for deceased potential participants were not warranted.

D.5. Success of the CATI Component

Despite significant obstacles, the CATI component of the study was quite successful, not only in terms of completion of interviews, but in the success of the programming and logistical aspects of the CATI. Because no existing CATI software was available which would accommodate the needs of the dosimetry system, it was necessary to identify software that would be suitable for creating a custom interview to satisfy the requirements of the HTDS. This task was undertaken by Mr. Mark Saporito, Systems Analyst and Programmer for the HTDS, using the INGRES relational database program. While developing such a program required extensive lead-time and testing, it also allowed for a system which could be completely matched to the needs of the study, both in terms of the type of information gathered and the use of the cognitive interview.

The idea of using a cognitive approach added significantly to the development time of the CATI as well. Because the data being sought were from such a distant time period and revolved around fairly mundane activities of daily living, the cognitive approach was extremely important in eliciting accurate information from respondents. There was, however, an equally important need to refrain from prompting the respondents' answers too much. Thus, careful and extensive planning, and advice from multiple consultants was used to ensure that the cognitive materials provided would not "lead" the respondents to give certain answers merely because they felt that was what the Interviewer expected.

The CATI dosimetry system developed for use in the HTDS was quite successful in providing a relatively smooth process for the interviews. The staff was successful in identifying appropriate

respondents, and completing interviews when a respondent was available. While there is no way to check the accuracy of the data elicited, the interviewers felt confident that most respondents were able to give responses which accurately reflected their recollections of the experience of the study participants.

E. Scheduling

E.1. Background

Prior to the initiation of the study it was believed that study participants would be widely distributed, with those who had moved away from eastern Washington living primarily in major urban centers in the West and throughout the country. The clinic location sites proposed in the study protocol, therefore, included sites throughout the Pacific Northwest as well as thirteen urban areas across the United States. Once the tracing component of the study began, however, it quickly became apparent that the majority of potential study participants lived in the Pacific Northwest. This made it possible to plan to hold almost all of the clinics within Washington State, with many participants driving to the clinic nearest their home. Those living outside the state could then be flown to Seattle to the clinics held at the FHCRC. Thus, three primary clinic sites were selected to accommodate the majority of study participants: Seattle, Pasco, and Spokane. Additional clinic sites in Walla Walla, Yakima, Wenatchee, and Omak were planned so participants living in these areas would not have to travel as far to attend a clinic. Although one two-day clinic was held in Portland, Oregon early in the study, subsequent clinics for Oregon residents were held in nearby Vancouver, Washington.

There were several advantages to being able to hold nearly all of the clinics within Washington State. First, HTDS could offer all participants a number of different clinic locations in the Northwest. If one location was not convenient, there were others, also relatively close. Second, clinic directions and maps to participants did not have to be constantly re-developed, and there was less potential for error in communicating directions to the participants. Third, many participants located outside the Northwest found the city of Seattle to be an excellent choice for a vacation, and planned their clinic visit to coincide with their vacation plans. Scheduling participants from out of state was also easier. Rather than waiting for all out-of-state participants to be located before scheduling clinics in other regions, they could be brought to Seattle throughout the study, or to other clinic sites, if that was desirable. In addition, holding all clinics in Washington State assisted the blinding of HTDS physicians to residence histories of participants, as it could not be assumed that those living in other states had been less exposed.

The timing and distribution of clinics was determined jointly by the Participation Coordinator and Field Operations Supervisor. As cohort members were located by the Tracing staff, recruiting and CATI efforts were focused so that pools of potential participants for a clinic would be large enough to support full clinic operations. In this way, the clinics could be scheduled at or close to capacity, and more clinics could be scheduled in areas with larger numbers of participants recruited.

A policy was established to provide reimbursement and offer assistance with arrangements for a number of special needs: 1) foreign language interpreters for non-English speaking participants; 2) sign language interpreters for the hearing impaired; 3) personal assistant or companion for participants with a physical or cognitive impairment; and 4) security assistance for participants incarcerated within Washington State. Other special needs were assessed as necessary, and decisions made on a case-by-case basis.

E.2. Objectives of Scheduling

The primary objective of the scheduling activity was to provide each participant with at least three options for clinic attendance, with the least possible inconvenience to the participant. For those participants within driving distance of a clinic, this included providing mileage and meal reimbursement allowances, as well as hotel allowances in the case of overnight trips. For those requiring air travel, all travel arrangements were prepaid by the study and made through FHCRC travel staff, or later, the study's Travel Coordinator, to minimize the inconvenience to participants who had to travel to attend a study clinic.

E.3. Final Process and Procedures

The Clinic Field Operations Supervisor and the Participation Coordinator developed a schedule of clinic dates and locations based on the current residences of participants. The clinic appointment was scheduled after the CATI, or after recruiting, if no CATI respondent was available.

Multiple attempts were made to contact all participants and each participant was offered several options for clinic dates. The Schedulers made calls to participants at varying times of the day and week. All participants, including those scheduled in the final few months of the study, were offered at least three options for clinics. Participants requiring air travel or overnight accommodations were called between 12 and four weeks in advance of the clinic date. Participants not requiring air travel or hotel accommodations could be scheduled up to two weeks before the clinic date.

A computerized tracking system was utilized for tracking the progress of participants through the scheduling process and for creating reports used to generate appointment confirmation letters. Each scheduled participant was sent a letter that included 1) the date and time of clinic appointment; 2) the location of the clinic and directions; 3) travel arrangements summary and/or tickets (if applicable) and 4) the Interview Preparation Worksheet.

If a participant canceled a clinic appointment, the Schedulers attempted to reschedule the participant as soon as possible. A participant who canceled a clinic appointment would be rescheduled an unlimited number of times. If a participant did not show up for a clinic appointment, without notifying the HTDS, the Schedulers attempted to reschedule an appointment. After a participant did not show up for three separate appointment times, no additional attempts were made to schedule the participant. Reminder calls were instituted to reduce the number of "no-shows" at the clinics. These calls were made one to three days prior to the clinic appointment. Based on previous experience with similar epidemiological studies, these reminder calls helped to reduce the number of participants who failed to show for their clinic appointment.

Despite concerted efforts, it was not possible to re-contact some participants after they had agreed to participate (either due to disconnected phone numbers or repeated attempts resulting in no answer or answering machines). In each case, attempts were made to obtain updated information from the CATI respondent (if one was available), through the initial tracing source, or by returning to the tracing staff for further tracing work. If these efforts did not obtain a current telephone number, a letter was sent to the participant requesting they contact us. If attempts to obtain updated information were unsuccessful, or if the participant did not respond to the letters or telephone messages, the participant was classified as "unable to schedule."

The Schedulers assessed the need for travel arrangements and, when necessary, would make the transportation, hotel and other arrangements for the participant. Schedulers followed specific guidelines for allowable travel expenses and reimbursements for participants. The Schedulers completed travel information forms for documenting travel plans.

If a participant decided not to participate in the study during the scheduling process, the Scheduler assessed the reason for the withdrawal and addressed the participant's concerns in an attempt to retain participation. If the participant persisted in the withdrawal, they were asked to complete a Refusal Questionnaire.

If a participant withdrew after agreeing on the first attempt, the decision to re-contact for a second attempt was made by the Scheduler and/or Participation Coordinator, based on the nature of the withdrawal. Second attempts following a withdrawal were handled in the same way regardless of the point at which the withdrawal took place.

E.4. Outcome

E.4.a. Results for the Pilot Study Sample

A total of 1174 Pilot Study Sample participants agreed to participate in the study, and 1063 (90.5%) attended clinics. These figures may differ slightly from those in the Pilot Study Final Report, since efforts to locate, recruit and schedule remaining Pilot Study participants continued throughout the Full Study.

Results in section V.C above, Recruiting, refer to the final agreement status of each participant at the end of the study. It should be noted, however, that some participants actually agreed to participate at the time of recruitment and withdrew from the study at the time of scheduling a clinic appointment. Table V.E-1 shows numbers of those who "Ever Agreed" to participate, those who "Withdrew" from the study prior to being scheduled to attend a clinic, and those who actually attended a clinic, for the Pilot Study Sample.

Table V.E-1. Success in Scheduling Potential Participants - Pilot Study Sample (N=1590)

Scheduling Status	No.	% of Ever Agreed (N=1174)	% of Agreed Excluding Withdrawals (N=1094)	% of Living/Located Pilot Subjects (N=1360)	% of Selected Pilot Subjects (N=1590)
Ever agreed to participate	1174	--	--	86.3	73.8
Withdrew	80	6.8	--	5.9	5.0
Agreed (did not withdraw)	1094	93.2	--	80.4	68.8
Attended clinic	1063	90.5	97.2	78.2	66.9
Unable to schedule*	31	2.6	2.8	2.3	1.9

* Those categorized as "Unable to schedule" are those participants who agreed to participate but attempts to re-contact the participant were unsuccessful. A few additional participants, although offered at least three clinic appointment choices, could not be scheduled before the end of clinics.

E.4.b. Results for the Transition Sample

Table V.E-2 shows numbers of those who "Ever Agreed" to participate, those who "Withdrew" from the study prior to being scheduled to attend a clinic, and those who actually attended a clinic, for the Transition Sample.

Table V.E-2. Success in Scheduling Potential Participants - Transition Sample (N=1005)

Scheduling Status	No.	% of Ever Agreed (N=749)	% of Agreed Excluding Withdrawals (N=692)	% of Living/Located Transition Sample (N=849)	% of Selected Transition Sample (N=1005)
Ever agreed to participate	749	--	--	88.2	74.5
Withdrew	57	7.6	--	6.7	5.7
Agreed (did not withdraw)	692	92.4	--	81.5	68.9
Attended clinic	664	88.7	96.0	78.2	66.1
Unable to schedule*	28	3.7	4.0	3.3	2.8

* Those categorized as "Unable to schedule" are those participants who agreed to participate but attempts to re-contact the participant were unsuccessful. A few additional participants, although offered at least three clinic appointment choices, could not be scheduled before the end of clinics.

E.4.c. Results for the Full Study Sample

Table V.E-3 shows numbers of those who "Ever Agreed" to participate, those who "Withdrew" from the study prior to being scheduled to attend a clinic, and those who actually attended a clinic, for the Full Study Sample.

Table V.E-3. Success in Scheduling Potential Participants - Full Study Sample (N=2604)

Scheduling Status	No.	% of Ever Agreed (N=1939)	% of Agreed Excluding Withdrawals (N=1778)	% of Living/Located Full Subjects (N=2141)	% of Selected Full Subjects (N=2604)
Ever agreed to participate	1939	--	--	90.6	74.5
Withdrew	161	8.3	--	7.5	6.2
Agreed (did not withdraw)	1778	91.7	--	83.0	68.3
Attended clinic	1720	88.7	96.7	80.3	66.1
Unable to schedule*	58	3.0	3.3	2.7	2.2

* Those categorized as "Unable to schedule" are those participants who agreed to participate but attempts to re-contact the participant were unsuccessful. A few additional participants, although offered at least three clinic appointment choices, could not be scheduled before the end of clinics.

E.4.d. Overall Results for the Entire Study

Table V.E-4 shows the final status of scheduling efforts for all those who agreed to participate in the study. Of those who agreed to participate, and did not withdraw from the study at a later time, 96.7% (3447 of 3564) attended a clinic. The rates for withdrawal (7.7%) and for those who did not withdraw but never attended a clinic (3.0%) remained fairly constant throughout the study.

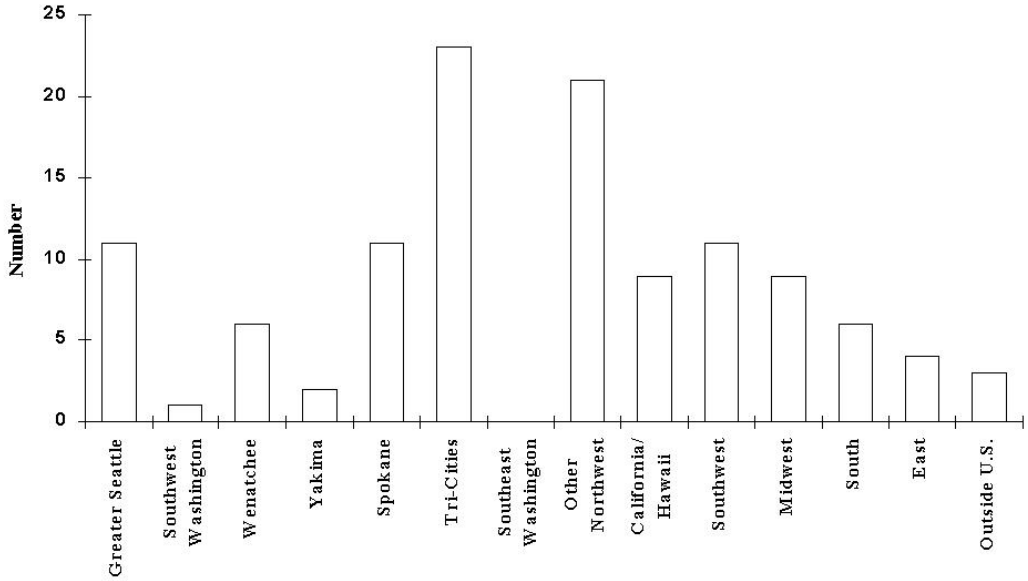
Table V.E-4. Final Success in Scheduling Potential Participants - Entire Study (N=5199)

Scheduling Status	No.	% of Ever Agreed (N=3862)	% of Agreed Excluding Withdrawals (N=3564)	% of Living/Located All Subjects (N=4350)	% of Selected All Subjects (N=5199)
Ever agreed to participate	3862	--	--	88.8	74.3
Withdrew	298	7.7	--	6.9	5.7
Agreed (did not withdraw)	3564	92.3	--	81.9	68.6
Attended clinic	3447	89.3	96.7	79.2	66.3
Unable to schedule*	117	3.0	3.3	2.7	2.3

* Those categorized as "Unable to schedule" are those participants who agreed to participate but attempts to re-contact the participant were unsuccessful. A few additional participants, although offered at least three clinic appointment choices, could not be scheduled before the end of clinics.

While it might be anticipated that those who declined to participate or could not be scheduled would most likely be those participants traveling the longest distances, this did not prove to be the case. It is likely that the popularity of the city of Seattle as a vacation destination and the diligent efforts of the Schedulers to coordinate participant's clinic appointments with their vacation plans, greatly reduced the number who would not attend a clinic due to travel requirements. Figure V.E-1 shows those who agreed to participate but never attended a clinic, by current area of residence.

Figure V.E-1. Subjects Unable to Schedule, by Geographic Area of Current Residence



Note: Southwest, Midwest, South and East regions are defined in section V.C.3.d.

The clinic sites used during the study, number of days at each clinic, and number of participants at each clinic are summarized in Table V.E-5. Approximately 50% of participants attended a clinic in Seattle. Pasco and Spokane were the next most commonly used clinic sites with 21.8% and 13.6% of participants, respectively.

Table V.E-5. Location and Number of Clinic Days and Participants Seen at each Site – Entire Study (N=3447)

Clinic Location	No. of Days at Clinic Site	No. of Participants Seen at Clinic Site	% of Participants
Seattle	133	1719	49.9
Pasco	60	753	21.8
Spokane	37	469	13.6
Vancouver, WA	22	295	8.6
Yakima	7	84	2.4
Walla Walla	4	46	1.3
Portland, OR	2	33	1.0
Wenatchee	1	17	0.5
Omak	1	16	0.5
Colville	2	15	0.4
Total	269	3447	100

The current residences of participants and the clinics they attended are shown in Table V.E-6. While most participants attended the clinic nearest their home, a number of participants attended a clinic in other areas. This occurred either as an incentive to participation (e.g., the participant wanted to travel to visit family) or due to difficulty scheduling the participant at a clinic in their area. The latter reason was most common in the smaller, more rural communities, where fewer clinics were held.

Table V.E-6. Current Residence of Participants by Clinic Site – Entire Study (N=3447)

	Clinic Site Attended								
Current Residence	Seattle	Pasco	Spokane	Vancouver, WA Portland, OR	Yakima	Walla Walla	Colville	Wenatchee	Omak
Greater Seattle	583	3	1	6	1	1	0	0	0
SW Washington	3	3	1	78	0	0	0	0	0
Wenatchee	11	19	23	0	6	0	1	16	15
Yakima	8	50	0	0	76	1	0	1	0
Spokane*	5	6	329	1	0	1	14	0	1
Tri-Cities	6	559	7	1	1	38	0	0	0
SE Washington	0	1	6	0	0	0	0	0	0
Other Northwest	117	80	79	220	0	5	0	0	0
California/Hawaii	318	10	3	10	0	0	0	0	0
Southwest US	237	12	7	3	0	0	0	0	0
Midwest US	164	4	6	4	0	0	0	0	0
Southern US	146	3	2	3	0	0	0	0	0
Eastern US	99	1	3	2	0	0	0	0	0
Out of US	22	2	2	0	0	0	0	0	0

* Includes the Colville area.

Note: Southwest, Midwest, South and East regions are defined in section V.C.3.d.

E.4.e. Conclusions

The process developed for scheduling participants proved to be extremely effective with nearly 90% of those who ever agreed to participate completing a clinic. The number of participants who withdrew after initially agreeing (298) was not unexpectedly high, considering the requirements of the clinical thyroid exam and interview, as well as the amount of travel required by many participants. The Schedulers arranged travel, including airline and/or hotel arrangements, for 1288 (37.4%) of the 3447 participants attending a clinic.

The participants who did not officially withdraw from the study, but who could not be scheduled into a clinic, were offered a minimum of three clinic options, and most were offered many more opportunities. In many cases, those in the category of "unable to schedule" and/or withdrew had multiple reasons for being unable to attend. These reasons included illness, unpredictable work schedules, and family responsibilities. Although some participants withdrew from the study during the scheduling process or were unable to be scheduled because of scheduling conflicts, many initially reluctant participants were persuaded by the scheduling staff to attend a clinic.

F. Clinical Evaluation

F.1. Background

F.1.a. Objectives for Clinical Evaluations

The objective of the clinical evaluation was to provide a thorough clinical examination of each study participant to identify the presence of thyroid disease or primary hyperparathyroidism. The evaluation provided data to determine the current presence or absence of disease for each disease endpoint. In addition, the clinic visit provided an opportunity for participants to ask questions and receive information about radiation and thyroid disease.

F.1.b. Rationale

The clinical evaluation provided information on each participant's current thyroid and parathyroid disease status. Prior to the examinations, each participant was asked to respond to an In-Person Interview (see section V.G.) which included questions pertaining to history of thyroid disease or hyperparathyroidism. The clinical evaluation included a thyroid ultrasound scan, independent thyroid examinations (palpation) by two physicians specializing in thyroid disease, and blood collection for thyroid function, parathyroid function, and anti-thyroid immune response tests. Additional studies were requested if indicated by the presence of palpable thyroid nodules. All costs associated with the clinical work-up, as well as travel to and from the clinic sites, were paid by the study.

F.2. Clinic Procedures

F.2.a Clinic Locations and Schedules

All clinics were held in Washington State, except for one 2-day clinic in Portland, Oregon. Conducting clinics in Washington provided efficiencies in equipment transport, planning, set-up, and staff travel. The clinics at the Fred Hutchinson Cancer Research Center in Seattle were primarily held on Friday and Saturday. Suitable clinic space was usually not available on Friday in other locations so clinics were most often held on Saturday and Sunday in locations other than Seattle.

F.2.b. Clinical Evaluation Process

Specific procedures for clinic operations were developed to optimize efficiency, assure all steps were completed, minimize waiting and maintain confidentiality. A packet was prepared for each scheduled participant containing consent forms and the data forms to be completed at the clinic. Participant names were written on index cards that were removed from the packets and transported separately for purposes of confidentiality and then re-attached to the packet at the clinic site. A clinic flow sheet was attached to the front of the packet. The clinic flow sheet provided an outline of each step or station to be visited and included a list of all data forms. The clinic staff person performing each clinic activity would check-off the completed activity.

Participants would first check in with the clinic coordinator and sign the study consent form (Appendix 12). The participant was then escorted to the In-Person Interview. After the interview, he or she was taken to the blood draw station. Following the blood collection, the nurse or phlebotomist answered any participant questions.

The next step was the ultrasound scan. The ultrasound scan was recorded on videotape, prints were made of key findings in the exam, and the sonographer completed a Thyroid Ultrasound Form

(Appendix 13). Following the ultrasound scan, thyroid exams were conducted separately by each of the two physicians at the clinic and the results recorded on Thyroid Examination Forms (Appendix 14). After the two independent exams, the physicians would confer. If there was disagreement between the examiners, they would perform another thyroid exam together to reach a consensus and complete a Consensus Examination Form (Appendix 15). After the two physicians reached an agreement on the exam findings and recorded the results, they reviewed the ultrasound scan results and the ultrasound scan prints. If there was any disagreement between the ultrasound scan and the physical exam results, a post-ultrasound consensus exam was done together by the two physicians and a Post-Ultrasound Consensus Examination Form completed. The physicians then conferred privately and discussed the results of the exams and the ultrasound scan. The physicians returned to the exam room to discuss the exam and ultrasound findings with the participant. A Thyroid Ultrasound Fact Sheet was given to all participants (Appendix 16).

If a fine needle aspiration (FNA) was indicated as a result of the exam or ultrasound scan, the physicians would discuss this recommendation with the participant and request consent to perform the procedure. FNA procedures were performed at any time throughout the day according to the participant's schedule or request.

The final step was a check-out with the Clinic Coordinator. The coordinator reviewed the clinic flow sheet to be certain that all steps were completed and checked that all data forms were completed. Travel reimbursement paperwork was completed at check-out.

At the end of the last clinic day, staff packed up all clinic supplies and equipment. Participant names were removed from the individual packets and the packets were transported to the HTDS office in a locked suitcase. Clinic staff transported serum specimens to the Pacific Medical Center Laboratory in Seattle and transported FNA specimens to the Laboratory of Pathology at Swedish Hospital in Seattle. Ultrasound videotapes were sent by messenger to Seattle Nuclear Medicine Associates.

F.2.c. Clinic Staffing

Clinic staff consisted of two physicians, one nurse or phlebotomist, one ultrasonographer, two or three interviewers, and a Field Operations Coordinator or Supervisor. Approximately fifteen potential participants were evaluated on each day. The dates and locations of clinics and staffing assignments were finalized 3-4 months in advance. To improve efficiency at clinics, various members of the clinic staff were trained and capable of performing multiple tasks. The Field Operation Supervisor was a certified phlebotomist and was trained to assist with FNA procedures. Both Field Operation Coordinators were trained in the In-Person Interview and one was also able to assist with FNA procedures. In addition, one interviewer was a certified phlebotomist, allowing her to assist the nurse or phelbotomist at peak times, or move to this position if needed.

F.2.d. Efforts to Reduce Physician and Ultrasonographer Bias

To ensure that the clinical decisions by the physicians and sonographers were not influenced by knowledge of the participants' possible exposures to Hanford ^{131}I, several precautions were taken during the clinical evaluation. The nurse or the phlebotomist asked participants not to speak with the physicians and sonographers about where they had lived, or about the possibility of their exposure to radiation from Hanford. Signs were also posted throughout the clinic requesting that participants not discuss these issues with physicians and sonographers. In addition, some participants who lived in towns where clinics were held were asked to attend clinics in other areas, so that physicians and sonographers would not associate participants at one clinic site with exposure and those at another clinic site with non-exposure. Finally, physicans were required to record at the end of their evaluation of each participant whether he had any indication fo possible radiation exposure for that individual. Of a total of 3440 evaluable participants,

there were only 15 instances where the physician had some suspicion that the participant might have had prior radiation exposure.

F.3. Serum Sample

F.3.a. Laboratory Studies

The Research Nurse collected a blood sample for thyroid function and other laboratory studies. A small number of persons refused to provide a blood sample. Such refusal did not affect the participant's eligibility for participation in the study or evaluability (see section IV.B above). Three 10 cc tubes of blood were drawn and centrifuged on site. The serum was transported within 72 hours to Seattle where one tube was frozen at -70 degrees Centigrade and stored as a reserve. The remaining two tubes were transported to the clinical laboratory at Pacific Medical Center in Seattle for the following studies:

- TSH (Thyroid Stimulating Hormone)
- FTI (Free Thyroxine Index)
- Antithyroid Antibodies
- Calcium

F.3.b. Changes in Laboratory Assays

F.3.b.1. AMA to Anti-TPO

Specific tests and assays changed throughout the course of the study, prompted by changes in the industry standard and on the recommendations from the laboratories.

The antimicrosomal antibody (AMA) assay was used initially to screen for autoimmune thyroid disease. Due to improvements in laboratory assays, the anti-thryroperoxidase (Anti-TPO) assay was available from Pacific Medical Center Laboratory in September 1995. At the request of the HTDS, the two assays were run in tandem until more than 500 assays had been performed using both methods. An analysis was performed to ensure the two methods were comparable, after which, the AMA was discontinued. The results of this analysis are shown in Table V.F-1 below.

Table V.F-1. Agreement between AMA and Anti-TPO Assay Results (N=677)

		Anti-TPO		
		Negative	Positive	Total
AMA	Negative	480	19	499 (73.7%)
	Positive	49	129	178 (26.3%)
	Total	529	148	677

These results indicate a high level of agreement (90%) between the two assay methods.

F.3.b.2. TSH Methods - RIA, EIA-1, EIA-2

The TSH test methods performed on HTDS serum specimens were done initially by radioimmune assay (RIA). The RIA method was used from November 1992 through January 1994. The RIA TSH method was changed to an ELISA immunometric assay (designated EIA-1) method starting February 1994. The EIA-1 method was used from February 1994 through August 1995. The EIA-1 method was modified to the EIA-2 method in September 1995. The EIA-2 method was used from September 1995 until the end

of the study in September 1997. In addition, the TSH normal range from the EIA-2 method was changed from a range of 0.47-5.01 units to 0.32-5.01 units as of Jan. 10, 1997.

F.3.b.3. Parathyroid Hormone Methods

Measurement of Intact PTH was done for all participants with an elevated serum calcium level. From the first clinic in November 1992 through October 1994, the Intact PTH test was done by the immunoradiometric assay. From November 1994 through the last clinic in September 1997, PTH was done by two methods, the IRMA and the Chemiluminescence methods. Separate calcium levels accompanied each method.

F.3.b.4. Anti-TG

In 1998 after the clinics were completed, anti-thyroglobulin antibody (anti-TG) assays were performed on serum samples that had been frozen and stored from the blood samples provided by HTDS participants at the study clinics. Although the anti-TPO antibody served as the highest quality assay for autoimmune thyroid disease, recent improvements in the anti-TG assay were available through Dr. Carole Spencer, an international expert in the measurement of antithyroid antibodies. These assays, which were performed in Dr. Spencer's laboratory, provided an opportunity to assess more fully the cumulative incidence of autoimmune thyroiditis in the HTDS cohort.

F.4. Inclusion of an Ultrasound Exam

The clinical evaluation included a thyroid ultrasound scan to detect thyroid nodularity. The decision to include an ultrasound scan in the clinical evaluation was based on three primary benefits: 1) there would likely be a small increase in the ability of the study to detect a radiation effect associated with clinical thyroid disease as currently defined; 2) nonpalpable thyroid UDAs abnormalities of the thyroid could be included as a study outcome variable and 3) the recorded ultrasound scan provided an objective record of the presence, location, and characteristics of thyroid growth abnormalities.

A certified ultrasound technologist performed the scan and was blinded to the participants' exposure status. The entire thyroid ultrasound scan was recorded on videotape. Physicians examined the participant without any knowledge of the ultrasound findings, then again after viewing printouts from the scan. Following the clinic, the videotaped scans were transported to Seattle for review by an off-site radiologist.

F.5. Ultrasound Follow-up Program

F.5.a. Purpose of the Ultrasound Follow-up Program

Participants at clinics who were found to have nonpalpable thyroid abnormalities seen only on the ultrasound scans were given a Thyroid Ultrasound Fact Sheet. This fact sheet explained the unknown clinical significance of the abnormal findings. In addition, these participants were invited to participate in the HTDS Ultrasound Follow-Up Program.

The Ultrasound Follow-Up Program was offered as a service to participants, and was not intended as a substitute for treatment or follow-up by participants' health care providers. The primary purpose of the program was to: 1) identify early nonpalpable, rapidly growing, thyroid cancers, and 2) provide referral assistance to facilitate appropriate management of participants' medical care.

Initially, there were two possible follow-up appointments for eligible participants. The first appointment was at 9 months after the initial clinic appointment and, if a change was detected on physical exam or ultrasound scan, a second follow-up appointment was recommended 6 months after that date. This second exam was a total of 15 months after the participant's initial clinic appointment. This design was modified in January 1994 to become a one-time follow-up appointment done 9-15 months after the participant's initial clinic appointment.

The original design of the follow-up program also included an examination by an HTDS physician. In February 1994, the physician examination was discontinued as part of the follow-up program. The purpose of the follow-up program was to detect changes in nonpalpable thyroid cancers. Since it was very unlikely that small changes in size could be detected by physical examination, it was decided that little useful information was provided by the follow-up physical exam. If a new or larger nodule was found on follow-up ultrasound exam, the participant was examined by a physician. A total of 260 participants were evaluated during the Ultrasound Follow-Up Program.

F.5.b. Discontinuation of the Ultrasound Follow-up Program

The Ultrasound Follow-Up Program was discontinued in June of 1995 for several reasons. In May 1995, a physician review of the data collected from the follow-up program revealed that no significant changes were found between the initial and follow-up ultrasound scans that would change the diagnosis or the recommended treatment or follow-up. Consequently, very little new diagnostic information had been collected from the follow-up program and no fast-growing cancers had been identified. The Ultrasound Follow-Up Program was not one of the HTDS research objectives and data from the follow-up exams and scan were not entered into the primary database. Therefore, discontinuation of the follow-up program did not affect the study's objectives.

The follow-up program became difficult to integrate into the busy HTDS clinic schedule. The follow-up program utilized the same ultrasound equipment and personnel as the HTDS clinics. An assessment of the clinic schedules indicated that the follow-up program would cause a significant delay in the completion of the HTDS clinical evaluations. Also, scheduling of the follow-up clinics was determining the dates and locations of HTDS clinics rather than consideration of new participants' residences.

An additional operational concern was the volume of work generated by the follow-up program. The Ultrasound Follow-up Program demanded substantial staff time and effort at clinics, and in the study office for follow-up appointment calls and letters, entry of tracking data, and physician review of the results and preparation of follow-up outcome letters to participants and their personal physicians. Continuation of the follow-up program would have required hiring additional staff and purchasing additional equipment.

In June of 1995, after consultation with the CDC and the HTDS Advisory Committee, the ultrasound follow-up program was discontinued. A special fact sheet was developed for health care providers and participants that provided information on the significance and management of patients with nonpalpable thyroid ultrasound detected abnormalities (UDAs).

F.6. Physicians

The study began with two HTDS physicians. In April 1993, four physicians were added to meet the demands of the full clinic schedule. All physicians were thyroid specialists. Physician pairings and clinic locations were rotated among physicians to reduce the potential for bias that might occur if the same physicians worked only at certain clinic locations.

A total of 3447 eligible participants attended a clinic, however, one participant did not have a thyroid exam due to a tracheotomy. Three of the 3446 participants who had a thyroid exam were examined by one physician, rather than two because of a scheduling problem. The numbers of participants examined by each pair of physicians is shown in Table V.F-2. Physicians #1 and #2 participated from the beginning of the clinical activity and continued throughout the study. As a result, 746 (21.6%) of the participants were examined by physicians #1 and #2, and 2822 (81.9%) were examined by a physician pair that included physician #1 and/or #2. The three participants examined by a single physician were all seen by physician #1 or #2.

Table V.F-2. Pairings of Physicians for Clinical Examinations*

		Second Physician				
First Physician	No Second Physician	#2	#3	#4	#5	#6
#1	1	746	285	322	367	198
	0.03%	21.6%	8.3%	9.3%	10.7%	5.7%
#2	2	--	332	423	66	82
	0.06%	--	9.6%	12.3%	1.9%	2.4%
#3	--	--	--	117	67	233
	--	--	--	3.4%	1.9%	6.8%
#4	--	--	--	--	26	141
	--	--	--	--	0.8%	4.1%
#5	--	--	--	--	--	38
	--	--	--	--	--	1.1%

* Entries in the table are the number (upper) and percentage of participants who attended the clinic and were examined by the indicated pair of physicians.

F.7. FNA Criteria

The original study protocol called for FNA procedures to be performed on study participants whose exams indicated the presence of discrete, palpable, solitary thyroid nodules or discrete, dominant nodules in a multinodular thyroid gland.

In February 1994 the criteria for conducting FNA procedures at clinics were expanded. In addition to nodules palpated on exam, the HTDS physicians also requested consent to perform FNA on participants who were found to have nonpalpable ultrasound detected nodules of 1.5 cm or greater (average of three dimensions) in a palpable thyroid gland. This modification was made after several participants were found to have quite large abnormalities detected by ultrasound that neither of the two experienced thyroidologists could palpate. The decision to attempt to perform an FNA on these large, ultrasound detected thyroid abnormalities was based on: 1) consideration of the HTDS physician's confidence of biopsying the nodule(s) detected by the ultrasound; 2) the physician's concern that the abnormality may represent a thyroid neoplasm; and 3) technical and safety aspects of performing a biopsy on a nonpalpable abnormality.

In some cases, the HTDS physicians recommended an FNA to a study participant after his/her clinic appointment. This recommendation was made as a result of the radiologist's review of a participant's ultrasound scan results.

In a very few cases, participants were recommended to undergo ultrasound-guided FNA as a safety precaution due to a nodule's close proximity to the carotid artery. In these rare instances, the

participant was referred to a medical facility near their place of residence that had the capability for ultrasound-guided FNA. The data collected from these procedures were used in the data analysis.

After review of the FNA biopsy results, each participant was assigned a diagnosis from the FNA or was recommended to have further evaluation. If the FNA was consistent with thyroid cancer (papillary carcinoma), the participant was recommended to see his/her physician for consideration of thyroid surgery. As discussed in section V.I below, all histology slides from such surgery were requested for review by the HTDS study pathologist and the diagnosis of either thyroid cancer or benign thyroid nodule was assigned depending on the pathology review. If the HTDS FNA result was adequate and consistent with a benign thyroid nodule, no further evaluation of the nodule was recommended, and the participant was recommended to follow-up with their personal physician. In these cases, the HTDS diagnosis was benign thyroid nodule.

If the initial FNA biopsy result indicated an intermediate or high probability of a follicular neoplasm (either benign or malignant), the participant was recommended to have further evaluation by his/her physician team, usually with consideration of thyroid surgery. These recommendations were made since FNA cytology cannot reliably distinguish between a benign follicular neoplasm (adenoma) and a follicular carcinoma. In these participants, no HTDS diagnosis was initially assigned but rather the participant was followed until the end of the study to await further diagnostic information, usually from surgery. When such information became available, the participant was then given an HTDS diagnosis of either thyroid cancer or a benign thyroid nodule depending on the outcome of the surgical diagnosis. For participants who (for whatever reason) did not go on to have thyroid surgery by the end of the HTDS field component (1997), definitive information to make a diagnosis on the nodule that was biopsied was not available. For the HTDS analysis, these individuals were classified as having a nodule "suspicious for follicular neoplasm". It is important to emphasize that none of the participants with this diagnosis had a nodule that was suspicious for papillary thyroid cancer but rather a nodule that had some probability of a follicular neoplasm. Since the majority of such lesions represent benign follicular adenomas, this category largely would be expected to represent benign nodular lesions. The following data from the HTDS illustrate this further.

Of the 259 evaluable participants who underwent FNA, 47 (18.1%) were recommended to have further biopsy or surgery. Of these 47, 12 were subsequently found to have thyroid cancer, five to have follicular adenoma, and 13 to have benign nodule other than follicular adenoma. The remaining 17 participants (6.6% of the original 259) were classified as suspicious for follicular neoplasm. All of these 17 cases were so classified because they did not go on to have further biopsy or surgery. For none of these 17 participants was there an actual clinical suspicion of papillary cancer. In fact all 17 had intermediate or high probability of follicular neoplasm based on their FNA results. Thus, for the 6.6% of the 259 persons who had FNA and were recommended to have further biopsy or surgery, we were not able to obtain further cytological or histological diagnoses. While the absence of such diagnoses makes it impossible to rule out the possibility of thyroid cancer, the probability of a benign lesion would be quite high given that all the 17 cases were suspicious for follicular neoplasm rather than for papillary carcinoma.

F.8. Thyroid Nuclear Scan Criteria

A thyroid nuclear scan and radioiodine uptake was recommended for three situations: 1) the results of an FNA indicated suspicious cytology which could be an indicator of an autonomously functioning nodule; 2) a neck mass was felt in the physical exam which was suggestive of an abnormality, but because of a technically difficult exam (e.g., a very obese neck), a consensus between examiners could not be reached at the clinic; and 3) for participants who had a suppressed TSH blood value and a normal or elevated FTI blood value to rule out a diagnosis of Graves Disease or a toxic thyroid nodule.

F.9. Training and Quality Control

F.9.a. Training

Two months prior to the first HTDS clinic, a "mock" clinic was held for staff training. HTDS staff assumed the roles of study participants and went through each clinic activity including the interview, blood draw, thyroid ultrasound scan and physical exam. Blood specimens were sent to the laboratory and analyzed to test specimen processing, transport, and other clinic procedures.

The mock clinic accomplished three primary objectives. First, the anticipated amount of time a participant would spend at each activity, and the total time at the HTDS clinic were verified to be consistent with the predicted total of two hours. The second objective was to test the designed clinic flow. The goal was to ensure the smooth and orderly transfer of participants through the various steps of the clinics, to avoid long waits, and to assure that each activity would be completed. The third objective was to give HTDS staff firsthand experience of the clinic activities to raise their awareness and ability to respond to participant questions and concerns about any part of the clinic experience.

The study ultrasonographers underwent additional training with Dr. Keith Wang of Seattle Nuclear Medicine Associates to standardize their technique of performing thyroid ultrasound scans. New sonographers were accompanied by the experienced HTDS sonographers for a minimum of two full days or until agreement in technique was obtained. During this training period, one sonographer performed the exam and recorded the results while the second sonographer recorded the findings on a second Thyroid Ultrasound form. The sonographers then switched places for the next participant. At the end of the clinic, the Field Operation Supervisor compared the findings for each participant, reviewed any discrepancies with both sonographers, and instituted further training as necessary.

F.9.b. Ultrasonographer Quality Control

A total of four certified sonographers worked on the study at various times but only one or two sonographers were on staff at any given time. An attempt was made to divide the clinical schedule evenly between the two sonographers on staff. In addition to the initial training, ongoing quality control procedures were undertaken to monitor inter-operator reliability. Approximately every two months, both sonographers would perform independent scans on each of five participants. The results of the scans were recorded on separate videotapes, the findings were compared and discrepancies were noted and discussed. Quality of sonography outcomes was monitored for each pair of sonographers that were currently sharing clinics. Results of the ultrasound quality control comparisons, based on a total of 103 participants, are summarized in Table V.F-3.

Table V.F-3. Results of Quality Control Ultrasound Studies

		A	B		No. of Participants		
Ultrasound Tech Pair	No. of Participants	No. of Nodules (>5 mm) Identified by Either Tech	No. of Nodules (>5 mm) Identified by Both Techs	B, as a Percent of A	With No Nodules (>5 mm) by Both Techs	With No Nodules (>5 mm) by Tech 1 but ≥1 Such Nodules by Other Tech	With >1 Nodule (5 mm) by Tech 1, but No Such Nodules by Other Tech
1 + 2	30	33	20	61%	16	1	1
1 + 3	25	27	12	44%	16	1	2
1 + 4	48	79	44	55%	23	1	4

F.9.c. Radiology Quality Control Program

A radiology quality control program was designed to monitor agreement rates among the radiologists interpreting the videotaped ultrasound scans. Six radiologists were initially identified to review and interpret the ultrasound videotapes for the HTDS. The radiologist assigned to read ultrasound scans for a particular clinic was determined solely by the radiologists' work schedules and availability. No effort was made to equalize the numbers of scans read by each radiologist. One radiologist interpreted the scans from the first clinic only, and one radiologist read scans only through the second month of the study. From early 1993 until the end of the study, four radiologists were involved in interpreting the HTDS ultrasound scans.

For purposes of quality control, approximately ten scans per month were sent back to the radiologists to be reviewed and interpreted a second time. These tapes were submitted along with scans from the most recent clinic. Comparisons between the two forms of abstracted findings by the radiologists were made to determine if significant changes could be identified between the first and second reading. A total of 343 ultrasound exams were interpreted twice. In most cases the second review was performed by a radiologist other than the one who originally reviewed the case. However, in a few cases, the quality control review was done by the radiologist who first reviewed the case due to the radiologists' scheduling. As shown in Tables V.F-4 through V.F-7, there were very high levels of concordance between the results of the original reviews and second review.

Table V.F-4. Radiologist Agreement on Presence of Any Nodule

	QC Radiologist			
Clinic Radiologist	Yes	No	Uncertain	Total
Yes	132	6	2	140
No	4	195	2	201
Uncertain	1	0	1	2
Total	137	201	5	343

Table V.F-5. Radiologist Agreement on Number of Nodules Less Than 5mm Average Dimension

	QC Radiologist			
Clinic Radiologist	0	<10	≥10	Total
0	289	4	0	293
<10	7	40	0	47
≥10	2	0	1	3
Total	298	44	1	343

Table V.F-6. Radiologist Agreement on Presence of Diffuse Abnormalities

	QC Radiologist		
Clinic Radiologist	Yes	No	Total
Yes	30	8	38
No	7	298	305
Total	37	306	343

Table V.F-7. Radiologist Agreement on Number of Nodules ≥5mm Average Dimensions

		QC Radiologist					
		0	1	2	3	≥3	Total
Clinic Radiologist	0	220	-	-	-	-	220
	1	-	69	-	-	-	69
	2	-	1	25	-	-	26
	3	-	-	-	9	1	10
	≥3	-	-	-	-	18	18
	Total	220	70	25	9	19	343

F.10. Outcome and Results

F.10.a. Results for the Pilot Study Sample

Table V.F-8. shows the number of Pilot Study participants completing each component of the clinic. A total of 1063 Pilot Study participants attended a clinic. All except four participants (99.6%) had blood drawn for thyroid function and other studies. Seventy-six of the 79 participants for whom fine-needle aspiration was recommended had the procedure performed. This represents a 96.2% consent rate for FNA, significantly higher than had been anticipated.

Table V.F-8. Summary of Clinic Participation - Pilot Study Sample

	Clinic Components Completed	
	No.	% [A]
Agreed to participate	1094	--
Attended clinic	1063	100
In-Person Interview	1063	100
Ultrasound examination	1063	100
Radiologist review of ultrasound	1063	100
Blood sample drawn	1059	99.6
All thyroid function tests performed and results obtained	1058	99.5
Thyroid examination by two physicians	1061	99.8
Thyroid examination by one physician	2	0.2

[A] Percentage calculated in relation to number who attended clinic.

F.10.b. Results for the Transition Sample

Table V.F-9 shows the number of Transition participants completing each component of the clinic. A total of 664 participants from the Transition Sample attended a clinic. All except one (99.8%) had blood drawn for thyroid function studies. Forty-three (97.7%) of the 44 for whom FNA was recommended had the procedure performed.

Table V.F-9. Summary of Clinic Participation - Transition Sample

	Clinic Components Completed	
	No.	% [A]
Agreed to participate	692	--
Attended clinic	664	100
In-Person Interview	664	100
Ultrasound examination	664	100
Radiologist review of ultrasound	664	100
Blood sample drawn	663	99.8
All thyroid function tests performed and results obtained	661	99.5
Thyroid examination by two physicians	663	99.8
Thyroid examination by one physician	1	0.2

[A] Percentage calculated in relation to number who attended clinic.

F.10.c. Results for the Full Study Sample

Table V.F-10 shows the number of Full Study participants completing each component of the clinic. A total of 1720 participants from the Full Study sample attended a clinic. All except four (99.8%) had blood drawn for thyroid function studies. Of the 149 for whom FNA was recommended, 140 (94.0%) had the procedure performed.

Table V.F-10. Summary of Clinic Participation - Full Study Sample

	Clinic Components Completed	
	No.	% [A]
Agreed to participate	1778	--
Attended clinic	1720	100
In-Person Interview	1720	100
Ultrasound examination	1719	99.9
Radiologist review of ultrasound	1719	99.9
Blood sample drawn	1717	99.8
All thyroid function tests performed and results obtained	1713	99.6
Thyroid examination by two physicians	1719	99.9
Thyroid examination by one physician	0	0

[A] Percentage calculated in relation to number who attended clinic.

F.10.d. Overall Results for the Entire Study

Table V.F-11 shows the number of participants from the entire study completing each component of the clinic. A total of 3447 eligible participants attended an HTDS clinic. Seven of these participants were judged non-evaluable (see section IV-B for definition of evaluable participant) following their clinic participation, one due to inability to perform a thyroid exam due to a tracheotomy, and six because of incomplete residence histories. Of the 3447 participants, 3439 (99.8%) had blood drawn for thyroid function studies, and 3446 had a thyroid ultrasound scan. Three participants were examined by only one physician due to scheduling difficulties. Of the 272 participants for whom FNA was recommended, 259 (95.2%) underwent the procedure, while 28 (96.6%) of the 29 participants recommended to have a nuclear scan complied.

Table V.F-11. Final Summary of Clinic Participation - Entire Study

	Clinic Components Completed	
	No.	% [A]
Agreed to participate	3564	--
Attended clinic	3447	100
In-Person Interview	3447	100
Ultrasound examination	3446	99.97
Radiologist review of ultrasound	3446	99.97
Blood sample drawn	3439	99.8
All thyroid function tests performed and results obtained	3432	99.6
Thyroid examination by two physicians	3443	99.9
Thyroid examination by one physician	3	0.1

[A] Percentage calculated in relation to number who attended clinic.

F.10.e. Conclusions

One indication of the success of the HTDS clinics is the excellent overall completion rates for each component of the clinical evaluation, particularly the FNA procedures. An emphasis was placed on establishing a caring and supportive environment for participants and reducing the level of stress to participants during the medical examinations.

G. In-Person Interview

G.1. Background

The standard In-Person Interview (IPI) consisted of questions designed to collect information about the following areas: 1) residences after age 15 to identify participants who may have received radiation exposure living near other nuclear facilities; 2) occupational history, to account for possible on-the-job radiation exposure; 3) smoking history; 4) medical and dental radiological procedures or radiation therapy after age 15 to complete the identification of radiation exposure to the thyroid from these sources begun in the CATI; 5) thyroid disorders after age 15 to complete the medical history begun in the CATI; 6) prescription drug history, to identify those persons whose thyroid disease may be a side effect of certain prescription medications, or who are now taking medications which could impact the results of thyroid assays performed at the clinic; 7) standard demographic questions; and 8) familiarity/bias questions to determine if a relationship exists between the answers given in the questionnaire, and the participant's knowledge or beliefs about the Hanford radiation releases.

The questions on the standard IPI (Appendix 17) covered the time period beginning after age 15 and extending to the present because detailed information about the subject from birth through age 15 was obtained in the CATI. However, since it was anticipated that a CATI respondent might not be available for all potential participants, an expanded version of the IPI (Appendix 18) was designed to also collect information from birth through age 15 that would have been provided by the CATI (see section V-D for more information regarding CATI).

G.2. Objectives of the In-Person Interview

The primary purpose of the IPI was to obtain information directly from the study participant about past occupational or medical radiation exposures, history of thyroid disease, and general demographic information. Most questions in the standard IPI pertained to the period after age 15 to the present because the CATI provided information about the period from birth through age 15. Participants who did not have a CATI were given an expanded version of the IPI for collecting key data for the period from birth to age 15. This expanded version of the IPI provided details about residence history and types of milk consumed which were necessary to estimate a Hanford radiation dose. The IPI was conducted before the participant completed the medical components of the thyroid clinical evaluation (ultrasound, blood draw, and physical examination) to ensure that the participant's responses would not be influenced by knowledge of exam results.

G.3. Development and Revision of the Questionnaire

A total of six versions of the standard and expanded In-Person Interviews were used in the three phases of the study. With the exception of a modification of the residence history questions following the Pilot Study, the differences between versions consisted of minor wording changes made for clarification purposes and deletion of questions determined to be unnecessary. Listed below is a summary of the revisions:

November 4, 1992	Original version
January 6, 1993	Wording changes for clarification; income categories in demographics section adjusted; change in the order of questions in the prescription drug section
December 20, 1994	Pilot Study Revisions: Information about residences asked after 1957 only for geographic areas near other nuclear production facilities or test sites; mother's residence history while pregnant

	was added to the expanded version for participants born after December 1944; questions on whether the participant had ever been diagnosed with hyperparathyroidism were added
June 28, 1995	Deleted questions about other names used by the participant, except those for whom historical medical records were being sought; deleted question on reasons why the participant thought they didn't know more about Hanford; minor wording changes in two areas of participant directions
December 11, 1995	Revised wording from "x-ray treatment" to "radiation treatment" in medical history section; modified the explanation of fluoroscopy for clarification

G.4. Procedures for the In-Person Interview

All interviews were conducted by trained and experienced Interviewers at the time of the participant's visit to the HTDS clinic. The interview was always completed before the thyroid examination to eliminate the possibility that the participant's answers to the interview questions may be influenced by the results of the thyroid exam. Prior to the initiation of the interview, each participant was required to read and sign a consent form agreeing to participate in the study.

An In-Person Interview Preparation Worksheet (Appendix 19) was sent to the participant two weeks before the clinic appointment. Participants were asked to complete the worksheet prior to attending the HTDS clinic, and to refer to this form during the interview. At the end of the interview, the worksheet was collected from the participant to be filed with the questionnaire.

Following each In-Person Interview, the interviewer recorded his or her subjective impression of the reliability of the data collected (High, Generally Reliable, Questionable, Unreliable) and the participant's level of cooperation (Very Good, Good, Fair, Poor).

Interviewers were not assigned to any particular clinics or counties, thereby reducing the potential for bias that might occur if area-specific assignments were made.

G.5. Training and Quality Control

Interviewers were initially trained by the same Field Operations Coordinator and experienced FHCRC interviewing personnel to assure uniformity and quality in the interviewing procedures. Training consisted of instruction in general interviewing skills, proper methods and timing of probing, detailed question-by-question instruction, and instruction on editing and callbacks. Training sessions included role-playing exercises. Interviewers pilot tested the questionnaires and worksheets and refined their skills by interviewing a small sample of volunteers. Training was supplemented by two manuals: 1) a general Interviewing Manual and 2) a Question-by-Question Manual for the standard and expanded versions of the In-Person Interview.

The Interviewers edited (reviewed) each questionnaire at the clinic site immediately after the interview was completed to assure all information was completely filled out and to identify discrepancies. The Field Operations Coordinator edited the interview a second time (over-edited) within 14 days of the date the interview was conducted. Re-contacting of study participants by the Field Operations Coordinator for clarification or missed questions was usually done within two weeks of the date of the original interview. The Field Operations Coordinator coded the questionnaires for data entry at the time of over-editing. A manual for coding of interviews was developed and documents the coding procedures utilized.

Call-backs to participants for clarification or additional information were limited to those instances where the HTDS Interviewer made an error, either by omitting a question or not adequately probing a question. Most decisions on whether to call back a participant for additional information relating to the residence history were discussed with a study investigator before contacting a participant to determine whether information obtained after the thyroid examination could be used.

G.6. Outcome and Results

At the conclusion of the study, a total of 3447 eligible participants had attended the HTDS clinic. No participants declined to complete an In-Person Interview. Review of the interviews resulted in identifying six questionnaires judged to have insufficient residence history information to calculate a dose estimate. These six participants were determined to be non-evaluable (see section IV.B for definition of evaluable participant). One participant was unable to complete the interview because of developmental disabilities, however the participant's father (who was unable due to illness to participate in a CATI) was mailed a modified version of the expanded interview and provided the dosimetry and In-Person Interview information in this manner. Some participants with developmental or other disabilities were accompanied during the interview by a family member or guardian, who aided in the interview process.

Table V.G-1 is a summary of standard and expanded interviews completed during each phase of the study. The passage of time and selection of participants from earlier birth years later in the study increased the use of the Expanded In-Person Interview in the Transition and Full Study Samples. Overall, 61% of participants completed the Standard In-Person Interview, while 39% completed the expanded version. The 2112 with a Standard In-Person Interview included eight participants who should have received the expanded version, as they had no CATI respondent. These eight participants were called back after the clinic to collect the additional residence history information that would have been collected in the Expanded IPI, in order to estimate their dose.

Table V.G-1. Summary of Standard and Expanded Interviews by Phase of Study

Version of	Pilot Study		Transition		Full Study		Total	
Questionnaire	No.	%	No.	%	No.	%	No.	%
Standard	750	70.6	427	64.3	935	54.4	2112	61.3
Expanded	313	29.4	237	35.7	785	45.6	1335	38.7
Total	1063		664		1720		3447	

G.7. Quality of In-Person Interview and Expanded In-Person Interview Data

Overall, the quality of the information obtained in the interview was judged by the Interviewers to be high. If the Interviewer assessed the quality of the data to be questionable or unreliable, then he or she recorded the reason for this determination and identified specific sections affected. Table V.G-2 shows the Interviewer's assessment of the reliability of the participant's responses to the standard and expanded versions of the questionnaire, as well as those Expanded In-Person Interviews used for dose estimation, i.e., excluding the interviews with insufficient residence history to calculate a dose estimate. Responses to the standard questionnaire were judged to be of high quality somewhat more frequently than those to the expanded questionnaire, but both versions were judged to provide high or generally reliable data in more than 95% of the interviews. Table V.G-3 shows the reasons for questionable or unreliable data. The most common reason was that the participant did not have a clear memory of the events in question. This reason was cited more often for the expanded version than the standard version. Approximately a quarter of the questionable or unreliable responses to both versions were due to an uncertain understanding of the questions by the respondent. All but a few participants were judged to have a very good or good level of cooperation (Table V.G-4).

Only 120 of the 3447 In-Person Interviews (both Standard and Expanded) were judged to have data of questionable, unreliable, or unknown reliability. Of these, 65 were used for dose estimation purposes. Note that in Tables V.G-2, V.G-3 and V.G-4, the third column, Expanded IPI Used for Dose Estimation, includes the eight participants mentioned above who had a Standard IPI at the clinic but should have received an Expanded IPI.

Table V.G-2. In-Person Interviewers' Assessments of Reliability of Responses

	Standard IPI		All Expanded IPI		Expanded IPI Used for Dose Estimation	
Reliability of Responses	No.	%	No.	%	No.	%
High	949	44.9	411	30.8	407	30.9
Generally reliable	1110	52.6	851	63.7	845	64.2
Questionable	49	2.3	61	4.6	59	4.5
Unreliable	1	0.0	2	0.1	2	0.2
Unknown	3	0.1	4	0.3	4	0.3
Expanded IPI done, data not used	--	--	6	0.4	--	
Total	2112	100	1335	100	1317	100

Table V.G-3. In-Person Interviewer's Assessments of Reasons for Questionable or Unreliable Information

	Standard IPI		All Expanded IPI		Expanded IPI Used for Dose Estimation	
Reason	No.	%	No.	%	No.	%
Unclear memory of events	16	0.8	34	2.5	34	2.6
Uncertain understanding of questions	15	0.7	15	1.1	15	1.1
Hurried responses	3	0.1	2	0.1	2	0.2
Other	16	0.8	12	0.9	10	0.8
Not applicable*	2062	97.6	1272	95.3	1256	95.4
Total	2112	100	1335	100	1317	100

* Reliability of Responses was High, Generally reliable, Unknown, or Expanded IPI done, data not used

Table V.G-4. Interviewers' Assessments of Respondent's Cooperation

	Standard IP		All Expanded IPI		Expanded IPI Used for Dose Estimation	
Respondent's Cooperation	No.	%	No.	%	No.	%
Very good	1703	80.6	1021	76.5	1011	76.8
Good	382	18.1	278	20.8	277	21.0
Fair	22	1.0	26	1.9	25	1.9
Poor	3	0.1	0	0.0	0	0.0
Not answered	2	0.1	4	0.3	4	0.3
Expanded IPI done, data not used	--	--	6	0.4	--	--
Total	2112	100	1335	100	1317	100

More than 90% of participants at least partially completed an Interview Preparation Worksheet prior to the interview.

The residence history in the Expanded IPI presented the most recall difficulty since participants were quite young at the time. Codes referred to as "fuzzy date codes" were assigned to each residence in the birth through 1957 section of the interview. The codes indicate the precision with which the participant was able to specify the date of a residence change (i.e. within two months, within three months, plus or minus 6 months, a year or more). This allowed coding of inexact responses to date questions to standard mm/yy codes. For example, responses such as "in the fall of 1947" and "1952 or 1953" would be coded as 10/47 and 1/53, respectively. These and other coding rules were contained in a written Coding Manual.

G.8. Conclusions

A complete In-Person Interview was obtained from all except six of the 3447 eligible study participants attending an HTDS clinic. These six non-evaluable participants were judged to have insufficient information in the residence history section of the expanded interview to calculate a dose estimate. The interview data were obtained easily and few modifications of the questionnaire were needed throughout the study. The Interviewers judged the responses to be Highly or Generally Reliable in over 95% of the interviews.

H. Medical Review and Final Diagnosis Determination

H.1. Background

H.1.a. Objectives of Medical Review and Final Diagnosis Determination

The objectives of the medical review and final diagnosis determination processes were: 1) to evaluate each participant's HTDS clinical thyroid evaluation results; 2) to communicate results of the clinical evaluation to participants in a timely manner and, with permission, to communicate the results to the participant's health care provider; 3) to assign the final diagnoses for each case according to the format developed (see Appendix 20) using all information available prior to and including the HTDS clinical evaluation.

H.1.b. Rationale

A large amount of information was collected for each study participant from the interview and clinical evaluation. This information included serum laboratory results; ultrasound exam, physical examination and for some participants, FNA results, thyroid nuclear scans and medical records. Members of the HTDS clinic team met in regular sessions to review the clinical information for study participants. The purposes of these reviews were to determine final diagnoses and to plan the letters and telephone calls for communicating the results to the participants and their health care providers. After all diagnostic information was assembled and the Medical Review was completed, Dr. Hamilton completed a Final Diagnosis Determination Form. This data form was used to record all of the final thyroid, parathyroid, or ultrasound outcomes of the HTDS diagnostic evaluation.

H.2. Medical Review and Final Diagnosis Determination

H.2.a. Medical Review Process

The results from the laboratory assays, cytology interpretations and radiologists' reviews of ultrasound tapes were received in the HTDS office within 5-6 days after the HTDS clinic. Results and review forms were assembled for each clinic participant for the weekly Medical Review session. The staff participating in the Medical Review included Drs. Hamilton and Griep, the Research Nurse, and the Field Operations Supervisor (FOS). During the review, the FOS completed tracking data forms for the Medical Review. Dr. Hamilton reviewed participants with no abnormal findings, while both Drs. Hamilton and Griep reviewed those with abnormalities.

All participants underwent a post-clinic Medical Review of the HTDS clinical evaluation results within two weeks of the clinic appointment. During the review session a letter to report the results of the evaluation was developed for each participant, plans were outlined for communicating abnormal results to participants, and a determination was made as to whether further diagnostic procedures or treatment should be recommended. If the participant did not report any history of thyroid disease during the In-Person Interview, a final diagnosis assessment was made and a Final Diagnosis Determination Form was completed as part of the Medical Review process. If a participant reported a past history of thyroid disease during the In-Person Interview, medical records were requested and the final diagnosis determination was deferred until after those records were obtained, abstracted, and reviewed.

H.2.b. Additional Tests

The first step in each participant's review was to determine whether any recommendations for further testing were necessary to confirm or rule out a diagnosis. Additional tests may have included: 1) thyroid nuclear scan (e.g. for Graves Disease or toxic thyroid nodule diagnosis); 2) repeat blood draw for additional tests such as parathyroid hormone in the case of elevated calcium; 3) repeat analysis of existing serum due to equivocal results; and 4) repeat thyroid FNA due to inadequate specimen.

An HTDS physician or the Research Nurse contacted participants needing additional tests by telephone to discuss the abnormal results, to answer questions, and to recommend the appropriate follow-up procedures. If consent had been given to contact the participant's health care provider, that person was also contacted to discuss the recommendations. Following this initial contact, the Research Nurse re-contacted each of these participants on a regular basis to determine if the recommendations had been followed, and to obtain consent for receiving results reports. If consent was obtained, medical records, cytology and pathology slides and reports were requested and reviewed in the same manner as historical records and slides. The tracking system was used to track the progress of recommendations for further procedures and the acquisition of outcome information.

Nuclear scans were arranged by the Research Nurse to be done at a medical facility most convenient for the participant. For additional blood tests, the participant's blood was collected at a local health care provider's office or the nearest medical laboratory and shipped to Pacific Medical Center Clinical Laboratory in Seattle for processing. The Research Nurse handled all arrangements for follow-up tests, shipping of specimens and payment of services.

H.2.c. Communication of Medical Review Results to Participants and Their Health Care Providers

After evaluating each participant's clinical information, the physicians drafted a letter to the participant outlining the results of the evaluation. The Data Control Technicians printed the letters and attached the laboratory results pages and appropriate fact sheets for each participant. If the participant's results were all normal, the results letter was mailed out immediately. The Research Nurse entered information about all cases with abnormal findings into a follow-up system for contacting by telephone and further follow-up as indicated. The results letters for the participants with abnormal findings were mailed after telephone contact by the Research Nurse. All participants received their results within 3-4 weeks after their clinic appointment.

Letters were also sent to each participant's health care provider if the participant indicated this was to be done and supplied the provider's name and address. The letters to health care providers included recommendations for follow-up monitoring and tests. The health care providers were also sent copies of the results letter and the fact sheets sent to the participant.

All participants who had an FNA recommended by the HTDS physicians were called by the Research Nurse or Dr. Griep on the day of the Medical Review. If the participant gave consent, the health care provider was also contacted by telephone to discuss biopsy results and to answer any questions. On the rare occasion when a repeat FNA was recommended, participants were called by Dr. Griep to discuss the results of the procedure.

If additional tests were recommended after the Medical Review, the results of these tests were reviewed at the next Medical Review session and a second results letter was mailed to the participant and his/her health care provider, describing the results of the follow-up tests.

H.2.d. Fact Sheets

Fact Sheets on various topics related to the HTDS clinical evaluation and results were developed and distributed to provide information to study participants. One fact sheet described the purpose and explained the results of the blood tests conducted as part of the clinical evaluation. A Physician Referral Resources handout was developed to help participants locate a health care provider for follow-up on conditions identified in the HTDS evaluation. A fact sheet explaining autoimmune thyroiditis, and a series of fact sheets about nonpalpable ultrasound-detected abnormalities of the thyroid were provided only to participants with these results. An Ultrasound Follow-up fact sheet was distributed to explain the follow-up program for persons with ultrasound-detected abnormalities of the thyroid. Following discontinuation of the Ultrasound Follow-Up Program in April 1995 (see section V.F.5 above), the Ultrasound Follow-up fact sheet was discontinued and an additional paragraph of information was added to the results letter to discuss the significance of nonpalpable ultrasound detected thyroid abnormalities. Later, a new fact sheet describing what was known about nonpalpable ultrasound-detected thyroid abnormalities was added to provide additional information for participants (and their health care providers) who had no other thyroid disease identified.

H.2.e. Final Diagnosis Determination

Findings from the HTDS clinical evaluation, and in some cases, historical medical records identified during the interview process (see section V.G), were reviewed to determine the participant's final diagnoses. The final diagnoses included information about thyroid and parathyroid outcomes (including basis for diagnosis) and ultrasound findings. Diagnoses for cases with no indication of thyroid abnormalities were made by Dr. Hamilton. Diagnoses for cases with any indication of an abnormality were made by consensus of Drs. Hamilton and Griep. The final diagnosis data were recorded on the Final Diagnosis Determination Form (see section IV.C above). Final diagnoses or disease outcomes were further defined by variables to indicate the quality and source of documentation on which the diagnosis was based.

Final diagnosis determinations were made based on the following information: 1) HTDS blood test results; 2) HTDS ultrasound results; 3) HTDS examination results; 4) previous thyroid disease or treatment with thyroid medication reported in the HTDS In-Person Interview or CATI; 5) current use of thyroid prescription medication reported in the HTDS In-Person Interview; 6) HTDS FNA results, if any; 7) HTDS-recommended diagnostic or surgical procedures, if any; and 8) historical medical records obtained by HTDS, if any.

The Final Diagnosis Determination Form underwent minor revisions during the first two years of the study. In July 1995 the following three significant changes were made: 1) the two outcomes for multinodular goiter based on being on thyroid medication or not, were consolidated into one category designated multinodular thyroid gland; 2) Graves Disease was added as a separate diagnostic outcome; and 3) the "basis for diagnosis" and "Histologic/Cytologic Type" sections for each diagnosis were expanded and standardized.

After these revisions, it was necessary to review and revise the Final Diagnosis Determination Forms for approximately 1376 participants whose diagnoses had been assigned on earlier versions of the form. Six staff members reviewed the original Final Diagnosis Determination Forms and transferred data to the new forms. Laboratory results from the clinical evaluation were reviewed and ultrasound findings documented for each case. If no diagnoses had been indicated (i.e., findings were normal) the revised form was considered complete after verification by a second staff person. Dr. Hamilton thoroughly reviewed the diagnosis determination for cases with findings varying from those originally documented and cases where at least one diagnosis had previously been identified.

H.2.f. Dating of Diagnoses

To perform analyses accounting for the potential effects of the Nevada Test Site exposure, diagnoses made before 1957 had to be distinguished from later diagnoses. Therefore a date was assigned for every diagnosis recorded on the Final Diagnosis Determination Form, corresponding to the date or age of that diagnosis. If there were medical records, or a prior mention of thyroid disease during the CATI or In-Person Interview, the subject's chart was reviewed to determine the date or age of diagnosis. Otherwise, if the diagnosis was based on findings at or as a result of the HTDS examination, the clinic appointment date was assigned as the date of diagnosis. When dates/ages were not specific, the midpoint of the range was assigned as the date/age of diagnosis.

H.3. Outcome and Results

H.3.a. Number of Cases Reviewed and Follow-up Procedures Recommended

The total of 3447 eligible participants underwent medical review. For 79.3% of these participants, the Final Diagnosis Determination Form was completed at the time of their Clinic Medical Review. The remaining 20.7% had either requests for historical medical records or post-clinic recommendations for further diagnostic procedures. For these cases, the Final Diagnosis Determination Form was completed after all the additional results or records had been received.

A total of 259 participants had FNA procedures performed at the HTDS clinic or on the recommendation of the HTDS physicians after the Medical Review. Of these 259 participants, the HTDS physicians recommended that 47 participants have further biopsy or surgical procedures to rule out a diagnosis of thyroid neoplasm, or were recommended to undergo close follow-up by their health care provider to monitor progression of a thyroid disorder. Another fifteen were followed for further diagnostic tests such as blood redraws or nuclear scans. In addition, 29 participants with thyroid nodules or suppressed TSH were recommended to undergo thyroid nuclear scan. Twenty participants had an abnormal calcium level and were recommended to have additional blood drawn and analyzed for parathyroid hormone (PTH) studies to confirm or rule out a diagnosis of hyperparathyroidism. Thirty participants were requested to have additional blood drawn due to abnormal or borderline thyroid function.

H.3.b. Conclusions

The Medical Review and final diagnosis determination processes were conducted efficiently and all participants received a thorough evaluation of the clinical results to determine the presence or absence of thyroid disease. Study participants were provided with their results in a timely and considerate manner and they were provided with recommendations for follow-up if a condition was identified.

I. Historical and Post-Clinic Medical Records and Specimens

I.1. Background

I.1.a. Objectives of Obtaining Medical Records

The primary objectives of the medical record component were to: 1) document thyroid problems reported by study participants and CATI respondents; 2) obtain any cytological or histological specimens from previous thyroid biopsies or surgeries for review by the study's pathologist; and 3) obtain the results (including histological specimens) of any further diagnostic or surgical procedures recommended by HTDS as a result of findings at the HTDS clinic. A secondary objective of the medical record component was to obtain cause of death information on all cohort members located deceased, and assign cause of death codes according to a standardized rubric.

I.2. Process and Procedures Used

I.2.a. Historical Medical Records

Information was obtained from both the participant and the CATI respondent for the purpose of obtaining historical medical records. During the CATI, respondents were asked to provide the names (and addresses, if known) of any physician who saw the participant for diagnosis or treatment of thyroid disease. Prior to the clinic appointment, the participant was sent a work sheet on which to list the names and addresses of their current physician and any previous physicians seen for diagnosis or treatment of thyroid disease. At the time of the In-Person Interview, the participant was asked to provide the names and addresses of physicians or institutions where they had been diagnosed or treated for thyroid or parathyroid disease, and to sign a consent form for the release of information from each of these providers. Information from the CATI was provided to the In-Person Interviewer in the clinic packet so that consent for any records identified only by the CATI respondent could also be obtained from the participant during the clinic visit.

All completed consent forms were returned to the office, where a Data Technician reviewed them for completeness. If the provider's address was unknown to the participant, attempts were made to locate a current address so the consent could be delivered. A letter requesting the pertinent records was generated to accompany each consent form. Copies of the consent forms were filed in the participant's medical record. If a current address for a provider could not be obtained, the original consent signed by the participant was filed in the record with a notation that the provider could not be located. A log of medical record requests was kept so that requests could be followed and further action taken if records were not received. Information regarding the request of medical records was updated in the study Tracking System.

Once records were received, they were given to the Medical Records Abstractor for review, organization, and abstracting of laboratory values. If specific records were found to be missing, the Abstractor relayed this information to the Data Technician, who re-contacted the provider for the information. Once the record was deemed complete for HTDS purposes, the abstract and records were filed in the HTDS medical record, and the study Tracking System was updated to indicate the case was ready for Medical Review.

During the Medical Review sessions (for cases with medical records), the Medical Records Supervisor and Dr. Hamilton reviewed each case and Dr. Hamilton assigned the proper final diagnoses.

I.2.b. Post-Clinic Medical Records

For those participants where HTDS physicians recommended further work-up or treatment based on the HTDS clinic findings, medical records documenting these procedures were also requested. At the time the recommendation was made, the Research Nurse asked the participant to give consent for the HTDS to obtain these records. Once signed consent forms were received (either at the clinic or through the mail, if the recommendation was made based on the results of clinic cytology or blood tests), they were handled in the same manner as those for historical medical records. Tracking of requests, however, was handled by the Research Nurse, who kept in contact with the participants throughout any further evaluation, to ensure that recommendations were adequately carried out, or that the participant fully understood the ramifications to their health if they chose not to do so. Once records were received, this information was entered into the study tracking system, and the records were flagged as ready for medical review.

I.2.c. Blinding the Reviewer to Radiation Exposure

References to areas in which the participant had lived were blocked out of any records prior to review by Dr. Hamilton so no inference of radiation dose could be made based on past residences. This blinding of radiation exposure was accomplished in the following manner. When a record was found to state that the participant was a "downwinder," had lived in the Hanford area (or an area away from Hanford), or had been exposed to radiation from Hanford, a copy of those records was made. The original was filed in a section of the HTDS medical record marked "Unused Information," and stapled with a cover sheet so it would not be read inadvertently. The exposure information on the copy was then deleted, and the blinded copy used in the Medical Review process by Dr. Hamilton. The participant's name was recorded in a logbook along with information identifying the records that mentioned exposure status.

A similar procedure was used for records that indicated the participant had undergone radiation therapy for malignancies other than thyroid. In cases where the participant or respondent reported thyroid disease in the participant, only radiation therapy for disseminated malignancies such as leukemia was blinded. For participants without any report of thyroid disease, only radiation therapy to the upper body was blinded, including any radiation for disseminated malignancies such as leukemia. Again, details on the blinded records were recorded in a logbook.

Upon instituting these procedures, it immediately became apparent that by only blocking out such references to radiation exposure, Dr. Hamilton might infer that all cases with sections censored had references to radiation exposure. Thus it was decided that some random blinding of records would need to be performed as well. For this reason, every seventh case with medical records was selected for random blinding. The information blinded in these cases was always completely unrelated to radiation exposure status or radiation therapy. For example, references to previous gallbladder surgery might be censored in one case; while in another, documentation of a motor vehicle accident might be censored. Again, the original records were placed in the "Unused Information" section, with the blinded copies used for medical record review.

I.2.d. Cause of Death Coding

For each potential participant located deceased, the death certificate or informant information was used to complete a Cause of Death Form (Appendix 21). In addition, the primary cause of death was coded using the ICD9-CM system. For those whose date of death preceded the use of the ICD9-CM system, the primary cause of death was also back-coded using the system in use at the time of death (Table V.I-1). See section V.B.4.d.3 above, for detail on the success in obtaining death certificates.

Table V.I-1. Systems Used for Cause of Death Coding

Coding System	Date Published	Dates of Use
International List of Causes of Death	1939	1940-1948
International Select Causes of Death	1948	1949-1955
International Classification of Diseases, Sixth Revision	1955	1956-1961
International Classification of Diseases, Seventh Revision	1962	1962-1967
International Classification of Diseases, Eighth Revision	1968	1968-1978
International Classification of Diseases, Ninth Revision	1979	1979-1997

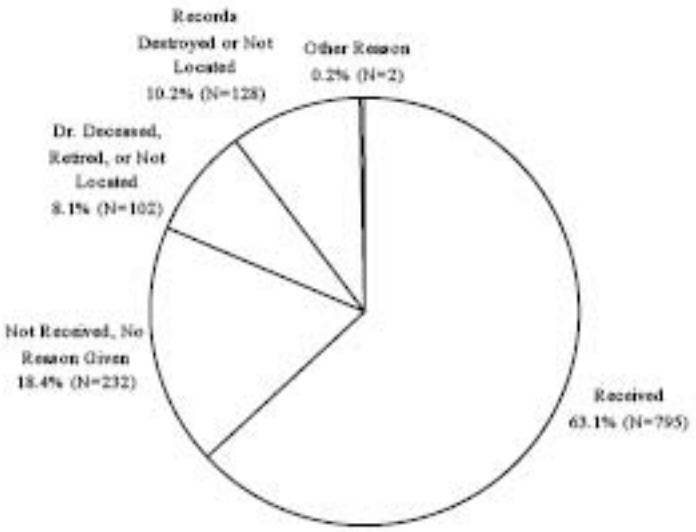
I.3. Outcome and Results

I.3.a. Historical Records

Reports of historical medical records were obtained for 694 participants, with a total of 1259 consent forms completed to obtain medical records from different providers. While the vast majority of reports were made during the In-Person Interview, CATIs yielded 30 of these reports.

Of the 1259 Medical Record Consents obtained, a total of 795 (63.1%) separate medical records were received by the HTDS. No records were received for 464 requests (36.9%). Figure V.I-1 shows the reasons for non-receipt of records. In 102 (8.1%) cases, records could not be requested because the physician was deceased, retired or a current address could not be identified. For 128 (10.2%) requests, records were unavailable due to the destruction of records, the inability of the provider to identify the patient, or an inability to locate the records. In 232 (18.4%) cases, records were not received after several contacts, without explanation as to why they were not available.

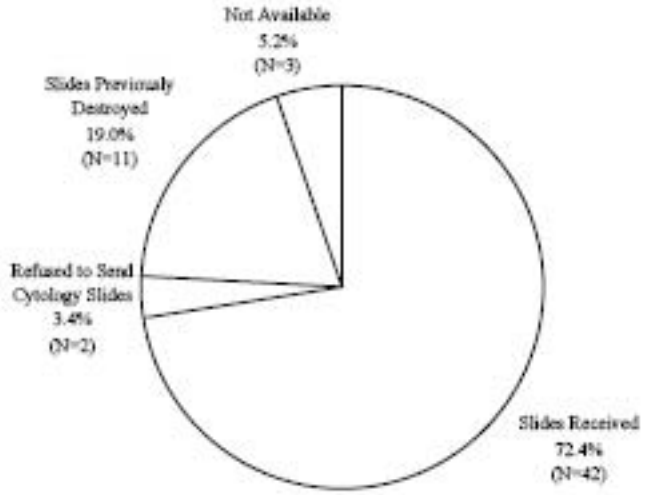
Figure V.I-1. Outcome of Historical Medical Record Requests (N = 1259)



I.3.b. Historical Pathology and Cytology Slides

Of the 694 participants identifying historical medical records to be requested, pathology or cytology slides were requested for 52 (7.5%). In a few cases, more than one set of slides was requested, for a total of 58 separate requests. A total of 42 sets of historical pathology or cytology slides were received for 42 participants (80.8% of those for whom slides were requested). Of the requests not resulting in receipt of slides, 11 were related to procedures performed prior to 1985 and the slides had been discarded, and three were not available. In the other two cases, cytology slides were not provided, as there would be no additional slides on file if they were lost or not returned. In these two cases, copies of the cytology reports were provided, and it was determined that the cytology appeared to be from the same nodules on which FNA had been performed at the HTDS clinics. Figure V.I-2 shows the success in obtaining historical cytology and pathology slides for review.

Figure V.I-2. Success Obtaining Historical Slides (N=58)



I.3.c. Post-Clinic Medical Records and Slides

Medical records documenting further diagnostic studies recommended as a result of the HTDS clinic findings were requested for 35 participants, with a total of 72 separate requests. All but one of these records was obtained, with at least one record obtained for each of the 35 participants. Thirty-three of these participants also had histology or cytology slides requested, for a total of 35 separate requests. All thirty-five of these specimens were obtained.

I.3.d. Cause of Death Coding

Cause of death was coded for 527 potential participants who were located deceased and 16 potential participants who were located alive but died prior to participation in the HTDS. Death certificates were received for 504 of the 543 total deceased potential participants.

In no case was thyroid disease listed as a primary or contributing cause of death on any death certificate obtained. In one case, the family member informant stated that the potential participant's cause of death may have been thyroid disease. However, the death certificate was obtained for this potential participant and the primary cause found to be malignant lymphoma.

I.4. Potential Impact of Medical Records and Slides That Were Not Obtained

One potential concern is that diagnoses of disease outcomes might be missed if requested medical records or slides could not be obtained: none or only part of the requested records or slides were received for 199 (29%) and 160 (23%), respectively, of the 694 participants for whom such requests were made. However, even if a medical record or slide could not be obtained, the likelihood of a missed diagnosis was generally low because in most such situations the HTDS evaluation provided a definitive assessment of whether the diagnosis for which the medical record or slide was sought was confirmed or not confirmed. For example, if a participant or CATI respondent reported a diagnosis of a thyroid nodule 30 years ago, that diagnosis would almost certainly be confirmed by HTDS physicians based on current physical exam and ultrasound scans. An exception would be for a participant reporting thyroid cancer, who then had thyroid surgery, and then had missing medical records. However, this occurred in only one individual**.**

To further clarify this issue, all of the diagnoses for participants with at least one missing medical record or slide were reviewed to determine which did not have a confirmed HTDS diagnosis and therefore might have been missed based on not receiving that medical record or slide. Of the 556 diagnoses for the 359 participants with at least one requested medical record or slide not obtained, 318 (57%) were confirmed by the HTDS evaluation. Of the remaining 238 diagnoses, 109 were diagnoses of hypothyroidism for which at least one requested medical record or slide was not obtained. Each of these 109 participants had normal thyroid function during the HTDS evaluation, thereby eliminating the possibility of permanent hypothyroidism. Of the remaining 129 diagnoses, 54 (16 with hyperthyroidism, 28 with simple goiter or multinodular gland, and 10 with "other" thyroid disease) were reported by or for participants who had completely normal HTDS thyroid evaluations. In addition, there were four miscellaneous reports of thyroid disease for which the HTDS evaluation was normal. For these 58 diagnoses the normal HTDS evaluation eliminates the possibility that these participants had permanent thyroid disease in these categories. Consequently, there were 71 diagnoses (13% of the 556 diagnoses) for which a missing record might have contributed to a diagnosis that was not confirmed by the HTDS evaluation. It must be emphasized however, that given the completeness of the HTDS clinical evaluation, this figure of 13% is likely an upper bound for the possibility of missed diagnoses related to any missing medical records.

Finally, it should be noted that the analysis of each thyroid disease outcome and of hyperparathyroidism included estimation of the dose-response not only for the definitive diagnoses based on HTDS evaluation or medical records with documentation supporting the diagnosis, but also for those based on less definitive criteria. In particular, these alternative analyses included diagnoses based on CATI respondent or participant reports only, which by definition had no confirmation from either the HTDS examination or from any medical records.

I.5. Conclusions

Attempting to obtain medical records and slides from as long ago as fifty years prior was expected to be one of the most difficult aspects of the HTDS. Many medical records are destroyed after only seven to ten years; physicians retire, sell their practices, or die, leaving little hope of locating historical records and slides. While no estimates of success in locating such records or slides was made in the HTDS Protocol, it was generally felt that records and slides would be obtained in no more than 50-60% of cases. While the experience of the HTDS was only slightly better at 63.6% of consents resulting in records or slides, it should be noted that of 694 participants with historical records or slides requested, 495 (71.3%) of participants identifying one or more records or slides had at least one record or slide retrieved. More recent

records and slides were retrieved more easily and, in many cases, these referred to earlier diagnoses for which the original records or slides could not be located. This enabled the study to confirm historical diagnoses in a greater percent of cases, despite the lack of older records.

J. Data Management

J.1. Objectives of Data Management

The primary data management objective was to establish procedures that would be used to develop and maintain the study databases, and the procedures that would be used to ensure data quality. These procedures included manual review (editing) of data recorded on paper forms, duplicate entry for all data forms, validity checks encoded in the data entry programs, and consistency check programs run on the data after entry.

The second data management objective was to define procedures to maintain the security and confidentiality of the data. This included data in computerized form, through the use of passwords and control of limited access to directories and data files, as well as hard copies of data, i.e., paper records, which were stored securely in locked files in locked offices or in a file room which had limited access via keycard.

The data collected for this study were classified into six main categories for purposes of data management:

1. Tracking system
2. CATI
3. In-Person Interview
4. Clinic Data Forms, Final Diagnosis Determination Forms, Refusal Questionnaires, Cause of Death Forms and Dating of Diagnoses
5. ICD9 Coding of Cause of Death
6. Problems Forms

The general principles guiding the development of data management procedures were the same for all six categories of data. These general principles included the use where appropriate of manual reviews (editing) of data originating on paper forms, duplicate data entry, automatic validity checks at data entry, additional computerized checks of data validity, frequent backups of computerized databases, password control of access to databases and of authority to update databases, and restricted access to physical repositories of data and specimens. The specific implementation of these general principles varied according to the nature of the data in each category, as described below.

At the beginning of the study, transfer of data between computers or from computers to back-up storage media was accomplished by means of removable media such as diskettes or tapes. Subsequently all of the study computers were connected to a local area network (LAN), and thereafter transfers and back up of data were managed through the LAN. The descriptions that follow describe the procedures that were adopted following availability of the LAN.

J.2. Data Management Procedures

J.2.a. General Procedures

Data were entered on personal computers which were linked via a LAN. Some data entry programs were stored on this network, in a directory with limited access. The LAN was backed up each business day by the network administrator.

To maintain confidentiality of the data, multiple levels of security were employed. First, the HTDS staff worked in a secure building with access to the floor limited to those with a security key card. The actual computers used for data entry were kept in locked offices and only authorized study personnel

had access to them. Most of the study computers were linked via a Novell local area network (LAN) and access to the data entry programs located on the local area network was limited via user names. The data files stored on the network were backed up daily Monday through Friday by the network administrator. All other data entry files were backed up daily when in use on floppy diskettes.

A password program was installed on all study computers. The password was changed whenever an employee left the HTDS or periodically during times when there were no staffing changes. As an additional security measure when an employee left the study, the network administrator revoked access to the local area network. A final security measure utilized was to keep all completed study forms in locked files or in a fileroom with limited key card access.

Preprinted labels with the participant's unique identification (ID) number were attached to each of the participant's forms to prevent transcription errors.

J.2.b. Tracking System

The tracking system contained data regarding the progress of participants through the study. These data were used by study staff to ensure the prompt and complete progress of potential participants through the various components of study participation: recruitment, identification of a CATI respondent and completion of the CATI, clinic scheduling, completion of clinic activities and recommended follow-up procedures, medical records requests, and completion of medical review and participant contacting. The tracking system database was written using dBase IV software as a menu driven program consisting of eight databases linked by the participant's ID number and last name. Table V.J-1 gives a brief description of the eight databases in the Tracking System:

Table V.J-1. Tracking System Databases

Database	Description
Overall	Summary of each potential participant's status.
Tracing	Tracing outcome, vital status, and death information.
Participation	Agreement/refusal/withdrawal information.
Dosimetry	Information regarding the CATI respondent and agreement and completion status of the CATI. Contains more than one record for some participants.
Clinic	Clinic appointment information and completion of individual clinic items.
Miscellaneous	Information regarding blood re-analyses, nuclear scans and repeat FNAs. Contains more than one record for some participants.
Medical Records	Information regarding medical records requests. Contains one record per medical record request, and thus has more than one record for some participants.
Participants	Participant's name and identification number.

Data entry programs for the tracking system were written to be user friendly, with all appropriate instructions on the screens as needed to enhance ease and accuracy of use.

Entry of data into the tracking system was not done in duplicate. Duplicate entry turned out to be impractical, and was deemed unnecessary in part because these were not outcome data. However, a program was run on these data periodically to check for invalid or inconsistent data.

Information about located potential participants was initially entered into the Tracking System on a weekly basis by a Data Technician, using data received from the Tracing staff in the Tri-Cities. Once the data for the week were entered, an electronic mail message was sent to key HTDS staff alerting them that the Tracking system had been updated, and noting any special circumstances for the new potential participants, who were identified only by ID number. As the various steps involved in contacting, recruiting, identifying a CATI respondent and completing the CATI, and clinic scheduling of a potential participant were accomplished, study staff created and updated records in the appropriate Tracking System data bases.

Following each clinic, the list of participants attending, and the steps of the clinic process completed by each participant were entered into the system by the Data Technicians. For participants who identified historical medical records, or for whom additional post-clinic studies were recommended, records were created in the Tracking System to track the request and receipt of these data, and to flag cases as ready for Medical Review.

J.2.c. CATI

A Computer Assisted Telephone Interview (CATI) was used for data entry of the dosimetry questionnaire on a real-time basis during the interview. The data entry program for this interview was written by the study programmer using the INGRES database software. Since the responses received during the CATI were entered directly into the database, they were not verified by duplicate data entry. One section that was handled somewhat differently was the residence history section, which was sent to the CATI respondent prior to the telephone interview. In most cases, the residence history was returned and data entered prior to the actual telephone interview, and then reviewed in the course of the interview.

The CATI database was programmed with automatic range checks, as well as skip patterns, where appropriate. (In the process of creating the scenario files used for dose calculations, additional consistency checks were run on the CATI data.)

At the end of each day during which they performed CATIs, each Interviewer copied the CATI database from his or her data entry computer to the network. This computer was equipped with a tape backup unit and software capable of making unattended backups at pre-selected times. See section VI Dose Determination, for more details regarding the CATI data.

J.2.d. Clinic In-Person Interview

The In-Person Interviews were completed and reviewed (edited) by the Interviewers at each clinic. After each clinic, the Field Operations Coordinator again reviewed (over-edited) the interviews and coded all items except the grid locations in the residence history section. A data technician, using a map provided by Battelle PNL for this purpose, coded locations of residences from the Residence History. Once the locations were coded, the interviews were data entered and verified in an INGRES database by a data technician on a separate personal computer. The verification database included programmed range checks and appropriate skip patterns. Upon completion of verification, the interview data were copied onto the local area network. These data were then converted into SAS® databases using the software package DBMSCOPY. Programs were written in SAS® to perform additional consistency and edit checks.

There were two types of the in-person interviews: the Standard In-Person Interview (designed for participants for whom a CATI had been completed) and the Expanded In-Person Interview (designed for

participants for whom a CATI had not been completed). A total of six versions of the Standard and Expanded In-Person Interviews were used during the study. The differences between versions consisted primarily of minor wording changes, and when revisions to the questionnaire were made, the appropriate changes were made to the data entry program. After the Pilot Study, however, there was a major revision to the way the residence history questions were asked. See section V.G above for details of the revisions made to the questionnaire. Due to the major revision after the Pilot Study, new versions of the In-Person Interview database and data entry programs were created. When the data technician copied the files onto the local area network after this revision was in place, two new directories were used, one for the Standard and one for the Expanded version of the questionnaire.

J.2.e. Clinic Data Forms, Final Diagnosis Determination Form, Refusal Questionnaire, Cause of Death Form and Dating of Diagnoses

Eight data forms were completed as part of the clinic component of the study. These forms included: 1) Clinic Flow Sheet, 2) Thyroid Exam Form, 3) Consensus Exam Form, 4) Post Ultrasound Consensus Exam Form, 5) Ultrasound Form, 6) FNA Form (as needed), 7) Blood Test Results Form, and 8) Final Diagnosis Determination Form. The Refusal Questionnaire, completed for those who refused participation but agreed to answer demographic questions, the Cause of Death Form, and Dating of Diagnoses were processed in the same manner as the clinic component data forms and are therefore included in the following descriptions.

The data forms were entered and verified in SPSS data entry files. The data entry programs contained range checks as well as skip and fill rules. A data entry manual was written for each data form, and included step-by-step instructions for entering the data. These manuals also contained detailed information regarding the variable names, types, length, description, and valid codes, and outlined the skip patterns. At the back of each manual was a Decision Log, where the Data Entry Operator identified cases that required a decision regarding how to enter the data. The Data Supervisor or the Statistical Research Associate reviewed all entries in the decision log. The data entry manuals were stored in the Data Supervisor's office.

At the end of each month, the SPSS data entry files were converted to SAS® data files via DBMSCOPY software that was available on the local area network. The converted files were then checked for duplicate records and unverified records, and any problems found were corrected. These files were then appended to the master files, which contained all previously cleaned data. As these files were appended, they were also compared to the master files for duplicates, and any found were deleted. The master files were stored in a directory with limited access, so that only the Data Supervisor and Statistical Research Associate could make changes to the files.

After the files were appended to the master files, a series of SAS® programs were run to check for any inconsistencies in the data files, such as skip patterns, invalid values, etc. When an inconsistency was found, the original clinic data forms were visually checked and a SAS® program was written which made the appropriate corrections. Hard copies of all such programs were stored in a locked file cabinet in the Statistical Research Associate's office.

Most of the clinic forms underwent minor revisions during the course of the study, and when necessary, the data entry programs were revised accordingly after careful investigation to ensure consistency of pre- and post-revision data. More significant modifications are described below:

Clinic Flow Sheets: The clinic flow sheet was used to track the progress of participants through the clinic, and did not contain substantive information regarding participant characteristics, radiation exposure, or outcomes. Data entry of the clinic flow sheet was discontinued after the 5/20/95 clinic.

FNA Form: The FNA form was not originally planned to be data entered. However, it was determined that it would be of interest to know how many FNA procedures were performed by each physician and consequently the FNA forms were data entered. In addition, an FNA form abstract was developed and used for the few FNA procedures that were performed at the request of HTDS but by an outside physician. This form indicated the number of nodules aspirated by the outside physician. The ID number, date of FNA and number of nodules aspirated was entered, in order to count how many nodules were aspirated.

Blood Results Form: The blood test results were reported from the laboratory on their own standard form. The database and data entry programs were revised when necessary to accommodate changes in the laboratory's form or in the assays they performed. Additional data were entered by study staff to further characterize the laboratory results, including identifiers of reassays (initial result, or reassay of original specimen), TSH assay type (RIA, EIA-1, or EIA-2), and PTH and calcium assay types (IRMA or chemiluminescence). See section V.F.3 Clinics, for further information on the laboratory assays used.

Final Diagnosis Determination Form: This Form underwent significant revisions during the course of the study, and the last version was adopted on July 28, 1995. To ensure consistency of the data from this key form, a copy of the final version was completed for all participants, including those whose medical review results had been recorded on an earlier version of the form. Please refer to section V.H.2.e above for a description of the changes made to the Final Diagnosis Determination Form.

J.2.f. ICD9 Cause of Death Coding

The ICD9 Cause of Death Coding was entered into an Excel spreadsheet by the staff member who performed the coding and then verified and resolved any discrepancies. This spreadsheet was then converted into a SAS® datafile using the software package DBMSCOPY.

J.2.g. Problems Forms

Throughout the study, staff were encouraged to bring any procedural problems to the attention of the supervisors and the Study Management Team. To formalize this process, a Problems Form was created. This form was completed by the person(s) who identified the problem and given to the Administrative Coordinator, who was responsible for bringing it to the attention of the appropriate people to be involved in determining and carrying out the resolution. The Administrative Coordinator was responsible for tracking progress toward resolution of items on Problems Forms, and prepared a weekly summary of the status of the outstanding forms. This summary was reviewed by the supervisors at weekly meetings and was also given to the Study Management Team for review. As resolutions to each problem were decided upon, these were logged by the Administrative Coordinator and the resolution of the problem was recorded on the Problems Form.

J.3. Outcome and Results

J.3.a. Tracking System

Table V.J-2 displays the number of records in each of the tracking system databases.

Table V.J-2. Number of Records in Each Tracking System Database

Database	No. of Records
Overall	4346
Tracing	4883
Participation	4348
Dosimetry	4447
Clinic	4346
Miscellaneous	69
Medical records	1443
Participants	4385

J.3.b. CATI

A total of 2133 participants who attended the HTDS clinic had a CATI. Of these 2133 participants, 29 also had an Expanded In-Person Interview. An additional 135 potential participants had a CATI, but withdrew from the study before attending an HTDS clinic.

J.3.c. Clinic In-Person Interview

A total of 2112 participants had a Standard In-Person Interview at the clinic. In addition, 1335 participants had an Expanded In-Person Interview at the clinic. One of these participants had help from his/her father as well as a caregiver during the Expanded In-Person Interview.

J.3.d. Clinic Data Forms, Refusal Questionnaires, Cause of Death Form, and Dating of Diagnoses

Table V.J-3 indicates the number of each of the clinic data forms, Refusal Questionnaires, Cause of Death Forms and Dating of Diagnoses that were data entered and the number of people with at least one of these forms entered for the 3447 eligible participants who attended a clinic.

Table V.J-3. Numbers of Records in the Clinic Database, Refusal Questionnaires, Cause of Death Forms, and Dating of Diagnoses

	Data Entered and Verified	
	No. of Forms	No. of Participants
Clinic Data Forms		
Clinic Flow Sheet	1192	1192
Initial Blood Test Results	3439	3439
Thyroid Examination Form	6899	3447
Consensus Examination Form	3447	3447
Ultrasound Form		
▪ Ultrasonographer	3447	3447
▪ Radiologist	3447	3447
▪ Ultrasonographer QC	103	103
▪ Radiologist QC	343	329
Post Ultrasound Consensus Exam Form	3448*	3447
FNA Form	263	259
Final Diagnosis Determination Form	3447	3447
Additional Blood Test Results		
Thyroid Function Redraws	27	27
Calcium Function Redraws	20	20
Reanalysis of Clinic Panel	37	37
Reanalysis of Thyroid Redraw	0	0
Reanalysis of Calcium Redraw	1	1
Refusal Questionnaire	365	365
Cause of Death Form	543	543
Dating of Diagnoses	1258**	667

* Includes one participant with a second Post-Ultrasound Consensus Exam Form following review by the radiologist, which indicated a new nodule.

** Number represents total number of diagnoses assigned a date prior to the clinic appointment date.

J.3.e. Problems Forms

A total of 147 Problems Forms were completed during the study. Problems ranged from clerical scheduling issues to final diagnosis determination. Each problem was reviewed and possible solutions discussed by the appropriate staff. All problems on the forms were ultimately resolved.

K. Data Quality Control

In addition to the data management plans and procedures outlined in the previous section, additional steps were taken after data collection to ensure a high degree of data quality. These efforts included more extensive examination of the In-Person Questionnaire data, the CATI data, scenario file Construction, dose estimation, and computer programming. More detailed descriptions of these efforts follow.

K.1. In-Person Interview Questionnaire Data

Data from the In-Person Interviews were entered into four INGRES databases, one each for the original and the revised versions of the Standard and Expanded In-Person Interviews. Each database consisted of approximately 25 tables. The frequency distribution of each variable was examined to check for invalid codes or values. Data from questions involved in skip patterns, i.e., questions that that might or not be asked, depending on the response to another question, were also reviewed. If any problems were found, such as invalid codes or inconsistent skip patterns, the participant's questionnaire was reviewed and the correct code was entered into the database. The background table, which includes the participant's ID, date of birth, and date of interview, was compared to the tracking system database to assure that each study participant who completed an In-Person Interview was present in the background table. Participant ID number then linked all of the tables. The background table was used as a reference to confirm that participants had information in each table. Once all of the within-table and between-table checks were completed, the four databases were compared to check for duplicate ID numbers between databases.

The most frequent problems found as a result of reviewing the In-Person Interview databases included the following: (1) residence histories having multiple addresses with the same move-in and/or move-out dates, and (2) medical histories reporting an age at first medical procedure less than 15 years of age in the Standard In-Person Interview, which only asked about procedures after the age of 15. The questionnaires of participants with either of these data problems were reviewed and the database revised as needed. In addition, several database tables contained exactly duplicated records due to a programming error in the INGRES database structure. Finally, many extraneous records had been created when previous attempts to correct records in the databases resulted in the creation of new records, rather than overwriting of records. These duplicate and extraneous records were identified and deleted.

K.2. CATI Data

The CATI data were stored in INGRES databases, each consisting of approximately 65 tables. Quality control began within each table by reviewing the frequency distribution of each variable. If any invalid codes were found, the audiotapes of the pertinent interviews were reviewed and the database was corrected accordingly. Data from questions involved in skip patterns were checked for consistency. Once these within-table checks were completed, the log table, which contains the participant's ID number, date of birth and date of interview, was compared against the tracking system to assure that all participants for whom a CATI had been completed appeared in the CATI databases. This table was then used as a reference in the between-table checks. When possible errors or inconsistencies were detected, the audiotape of the pertinent CATI was reviewed and the CATI database was updated as needed. Once all of the within-table and between-table checks were completed, the two databases were merged to search for any duplicate participant ID numbers.

After the two CATI databases were merged into one database, a series of more in-depth computerized consistency checks were conducted. These included the identification of definite inconsistencies as well as suspicious data that weren't necessarily inconsistent. All definite and possible

inconsistencies were investigated by reviewing the audiotapes of the CATIs, and correcting the CATI database as needed. Below is a more detailed description of the additional checks that were performed.

- A comparison was made between the table indicating the types of milk consumed at each residence to the tables containing the actual milk consumption values, to ensure that only the types of milk specified for a particular residence were reported as having been consumed at that residence. Note that data from the table indicating milk types is not used in the dose calculation, since this information is implicit in the information about quantities consumed. It was known that CATI respondents sometimes changed their responses during the interview, and it was believed that when they did, the tables of actual consumption values of the various types of milk would be the most accurate. Many of the discrepancies detected resulted in revision in the table of milk types. However, this comparison also identified occurrences of a particular data entry error that occurred when the Interview sometimes neglected to zero out of the consumption of a given type of milk, when the discontinuation of that type of milk occurred at the time of a residence change. For example, a participant may have consumed raw cow's milk only at his or her first residence, but only processed cow's milk thereafter. In such a case the Interview should have changed the raw cow's milk consumption to zero at the time of the residence change, but didn't always do so. All of these data entry errors were corrected in the table of milk consumption values.

- The food and milk consumption tables, which contained information about quantities consumed during different time periods for each participant, were searched for overlapping time periods or duplicate change dates. This check was made for each type of consumption (milk, fruit, vegetable, and eggs), as well as for the brands of milk.

- Large changes in consumption of specific food and milk products were examined. A large change was defined to include any increase or decrease by more that a factor of ten in the consumption rate. In addition, to test check for errors that might have arisen from changes in the way a CATI respondent reported consumption rates, e.g., from units per day to units per week, the following additional criteria were defined: (1) a decrease (increase) by more than a factor of 6 in conjunction with a change in reported consumption from units per day to units per week (or from units per week to units per day, respectively), and (2) a decrease (increase) by more than a factor of 4 in conjunction with a change in reported consumption from units per week to units per month (or from units per month to units per week, respectively). Review of CATI audiotapes confirmed that many of these large changes were indeed reported by the CATI respondent. Consumption values that were erroneous due to mistaken entry of the consumption rate were corrected in the table of consumption values.

- Extremely large consumption values were checked for both participant's and mother's diets, for each type of food and milk product category separately, i.e., for glasses, other servings and products of milk for all types of milk consumed, and for raw vegetables, cooked vegetables, raw tree fruit, cooked tree fruit, raw vine fruit, cooked vine fruit, and free range chicken eggs. In addition, the totals for a particular type of consumption, i.e. processed cow's milk, raw cow's milk, total milk consumed, total fruit, and total vegetables were also checked for extremely large values. Descriptive statistics were calculated for each of these separate and combined categories, and records indicating very high consumption levels were identified. The pertinent CATI audiotapes reviewed, and the data were verified or corrected, as appropriate.

- Because consumption of contaminated goat's milk was expected to cause relatively large doses, the audio recordings of all CATIs with an indication of consumption of goat's milk were reviewed and the data verified or corrected as appropriate.

- The CATI allowed the respondent to report that consumption of a given food or milk product changed gradually over a defined time period, for example, from one glass of milk per day at age 6 months to 3 glasses per day at age 3 years. Such "gradual changes" were coded a particular way. All records that were coded to indicate a gradual change, but for which the consumption value did not in fact change, were investigated. Most of these were determined to be correct because the CATI respondent initially

indicated that a gradual change had occurred, but subsequently reported that the quantity consumed had remained constant. In the remaining instances the database was corrected as appropriate, after review of the CATI audiotape is necessary.

- To code a gradual change in consumption of a food or milk product that ended at the end of 1957 (the end of the period for which doses were estimated), the CATI interviewers entered data indicating a change in consumption on 12/31/57 or 12/30/57. (Since dietary data were not collected after that date, this served as a convention to indicate the end of a gradual change.) All other changes of consumption in the year 1957 were investigated to ensure that they weren't meant to indicate gradual changes, and to search for errors in the year of the change date. The CATI audiotapes were reviewed and the table of consumption values corrected as necessary. One CATI Interviewer was found to have consistently recorded gradual changes ending at the end of 1957 incorrectly, using a date other than 12/31/57 or 12/30/57. All the consumption change dates in 1957 in this Interviewer's CATIs that were revised to reflect gradual changes ending at the end of 1957, with the exception of those for which consumption changed either to or from zero, which were considered reliable indicators of nongradual changes.

K.3. Scenario File Construction

To examine the accuracy of scenario file creation, portions of selected scenario files, including the participant's diet and residence history and the mother's diet, were recreated by hand or by a computer program written by someone other than the programmer who created the original scenario files. The participant's diet portion of the scenario file was recreated by hand for approximately 10% of those with CATIs. Two-thirds of those chosen were among the participants with more than the median number of records in the diet portion of the scenario file, and one third from those with fewer than the median number of records. Also included in this group were all participants with a diagnosis of thyroid cancer who had a CATI.

The residence portion of the scenario file was also recreated by hand but for a smaller number of subjects, as this was much less complex than the diet portion. The mapping of residences was also checked for 26 participants (110 places of residence) and no errors were found. In addition, the encoding places of residence within the HEDR domain was tested by checking whether the encoded locations were within the state and county recorded from the CATI or Expanded In-Person Interview. Only 4 errors were found and corrected. There was an error found in the map book, which was prepared by Battelle Pacific Northwest Laboratories for use in determining residence codes. The residence codes in Kittitas county were incorrect as written and subsequently revised. This affected 11 HTDS potential participants, whose residence codes were revised accordingly.

The mother's diet portion of the scenario file was recreated via SAS® programming by a different programmer than the one who created the original diet portion of the scenario file. These two files were then compared.

When the recreations of scenario file data described above identified any discrepancies, the computer programs used to create scenario files were examined for errors of logic or coding, and modified as appropriate.

K.4. Dose Calculation

In order to check the process of scenario file creation and dose estimation, raw dosimetry data for 10 participants whose doses were based on CATI data were provided to an investigator at the CDC. Using that raw data, the CDC investigator created scenario files from those data, and used those scenario files as input to the CIDER program to calculate a set of dose estimates which were then compared to the original estimates calculated by HTDS. Initially, the CDC was not informed of any assumptions made by the HTDS in creating the scenario files, in order to test whether the assumptions she made were similar to those

of HTDS. After a preliminary comparison of the CDC and HTDS dose estimates, it was determined that the CDC used the library of reference diets defined in the HEDR model for persons who consumed commercial ("grocery") milk, while the HTDS used the reference diets for persons who consumed milk from family cows (see section VI.A.3.a below for further description of reference diets). Although the selection of reference diet library had relatively little impact on the estimated doses of participants whose diets were largely if not entirely specified in their CATI data, the grocery milk reference diet library was used by both CDC and HTDS in the subsequent comparisons.

There were several other issues, primarily concerning the handling of unknown or incompletely specified data, for which the CDC and HTDS made different assumptions. These are described in Table V.K-1 below.

Table V.K-1. Differences in Assumptions Used by CDC and HTDS

Issue	CDC	HTDS
Gradual change in consumption of a food, milk, or milk product	The time interval of the gradual change was divided into thirds. Consumption in the 3 resulting subintervals was as follows: First: C(begin), Middle: [C(begin)+C(end)] / 2, and Last: C(end), where C(begin) and C(end) denote the consumption levels at the beginning and end of the interval, respectively.	The time interval was split by year and the consumption in each interval was calculated by successively adding the quantity [C(end) –C(begin)] / (#intervals–1), where C(begin) and C(end) denote the consumption levels at the beginning and end of the interval, respectively.
Unknown food, milk, or milk product consumption quantity	If the quantity was known for some portion of the time, that amount was used to estimate the amount during the time when it was unknown.	Left as unknown (i.e. used CIDER defaults) with the exceptions of 1) other servings of milk or milk products was unknown, or 2) one component of fruit was unknown. For the former, an HTDS default was used, based on tables of median amounts consumed by age, sex, and types of milk consumed. For the latter, the unknown component was set to 0. If more than one component of fruit was unknown, the total was set to unknown.
Combination of milk products and fresh milk	Sum of fresh milk and milk product quantities	Sum of fresh milk quantity plus half of milk product quantity
% Local for vegetables when known for both raw and cooked vegetables	The higher of % local for raw vegetables and % local for cooked vegetables was used	The weighted average of % local for raw vegetables and % local for cooked vegetables was used
% Local for vegetables when unknown for at least one of raw and cooked vegetables	Used 50%	Used 100%
Milk Brands – Brand unrecognized by CIDER	Used brand code	Set to grocer milk
Milk Brands – When brand records start after the milk start date	Assumed first reported milk brands applied from milk start date	Used CIDER default milk brand from milk start date until start of reported milk brands

Despite the differences listed in the table above, the CDC dose estimates were relatively close to those of HTDS, differing by less than 5% for half of the ten, and by less than 20% for eight of the ten; see Table V.K-2 below.

Table V.K-2. Comparison of Dose Estimates by CDC and HTDS

	Estimated Dose (Median of 100 Realizations, in mGy)		
Case	CDC	HTDS	% Difference
1	9.9	10.4	–5.1
2	9.1	9.2	–0.8
3	5.4	10.1	–46.2
4	35.8	25.0	43.1
5	2.5	2.7	–6.6
6	57.7	55.7	3.6
7	94.4	85.0	11.2
8	8.6	8.4	2.9
9	95.9	95.4	0.6
10	12.5	12.2	2.7

The difference in dose estimates for case #3 in Table V.K-2 (5.4 versus 10.1 mGy) was due to a misspecification of the participant's milk consumption in the HTDS estimate; this misspecification was corrected before the participant's final dose estimates were calculated. The difference for case #3 arose from a misspecification of the participant's wean date in the CDC dose estimate. The difference for case #7 resulted from the different methods of combining milk products and fresh milk (see Table V.K-1 above). In summary, this comparison indicated a high level of agreement between dose estimates calculated by HTDS and those calculated by investigators external to the HTDS who were left to devise their own assumptions regarding missing or incompletely specified information.

K.5. Computer Programming

The computer programs that involved major manipulations of the data or complex code other than standard SAS® procedures were reviewed or tested in various ways to ensure they were accurately doing what was intended. The computer programs that created files of outcome data, as well as those that created the files of data regarding the factors analyzed as possible confounding or effect modifying factors were reviewed by a second person. The dose-response programming was checked as follows. First, the Newton-Raphson algorithm used in these programs was written in Pascal. Using small test data files, the output was compared to hand calculations. In addition, a "fixed" data file, with doses and outcomes that would yield a known intercept and dose-response slope, was used to ensure the output was correct. When the HTDS data was used, the fitted values were examined to ensure they were reasonable. The program was first used for simple cases (e.g., one dose realization with one outcome) and then built upon to handle all 100 dose realizations plus three average doses (media, mean, and geometric mean) with multiple outcomes. Once this was completed, the program was written again using SAS® IML, and the output of the two versions compared. Throughout the process, matrix manipulations were performed to ensure they had the properties required of the Newton-Raphson algorithm.

The program to compute an estimated dose from Nevada Test Site exposures for each participant was written by the HTDS Programmer, using Fortran. Output from this program was compared to estimates obtained using the web-based tool provided on the NCI's website (http://rex.nci.nih.gov/INTRFCE_GIFS/radiation_fallout/radiation_131.html) for a small number of participants, to verify that the program and web tool provided the same results.

K.6 Mortality Data

Encoding of causes of death is described in sections V.I.2.d and V.I.3.d above. As a quality control check, text descriptions of causes of death from the death certificates or informant information were compared to the assigned cause of death code for the 543 potential participants for whom cause of death information was obtained. In 13 of 543 (2.4%) cases, the code was revised as a result of this review. In seven (1.3%) of the cases, the code was revised to 410 - Acute Myocardial Infarction from Another, Non-acute Cardiac Condition, in keeping with the coding rules regarding acute cardiovascular disease. In three (0.6%) of the cases, the code was revised from E995 – Injury due to War Operations by Other and Unspecified Forms of Conventional Warfare, to a more specific cause, due to identification of an additional information source on the exact cause of Vietnam war deaths. In one case (0.2%), the cause of death was changed from 770 – Other Respiratory Conditions of Fetus and Newborn to 760 – Fetus or Newborn Affected by Maternal Conditions Which May be Unrelated to Present Pregnancy. The remaining two revisions were due to data entry errors.

The programs written for the mortality analysis were also reviewed. Person-years at risk were calculated by hand and compared to the results of the computer program for selected participants. The numbers of living people in Washington State used in the mortality analysis program for the various sex, age group and calendar year categories were double checked by hand to ensure their accuracy. Similarly, the numbers of deaths in Washington State for specific causes of death and by sex, age group and year of death were also double checked by hand to ensure their accuracy.

VI. Radiation Dose Estimation

A. Background

A.1. Objectives of Dose Estimation

In an epidemiological study concerning a quantitative exposure such as the thyroid dose from Hanford's ^{131}I, the most informative analyses are likely to be those that examine the dose-response relationship in terms of individual measurements or estimates of exposure. When the initial planning of HTDS began, it was anticipated that the Hanford Dose Reconstruction (HEDR) Project, which was then well on its way to completion, would produce a system that could be used to estimate each study participant's thyroid radiation dose. The study design for HTDS was therefore built in part on the assumption that individual dose estimates would be available, although the design was intended to allow the study to succeed in the unlikely event that individual dose estimation was not possible. This assumption had several implications for the study. For example, it implied the need to collect information from which individual dose estimates could be calculated, which led in turn to the CATI component of HTDS. It also implied the need for the HTDS to establish a system that would process such information into a form suitable for use in dose estimation, accomplish the dose calculations, and make the results available for analysis.

The primary objective of this component of the study was to calculate individual estimates of radiation doses to the thyroid for HTDS participants. Specifically the estimates referred to doses to the thyroid from ^{131}I released into the atmosphere from the Hanford site, as calculated by the dosimetry system created by the HEDR Project. Secondary objectives included testing and verifying the accuracy of data that were used for calculation of dose estimates, and the production of data files concerning dose-related characteristics of the study participants, for use by the study statisticians. These data files would include both descriptive data regarding the participants, particularly concerning dose-determining characteristics, as well as data that might be used for alternative characterizations of exposure to Hanford's ^{131}I. An additional secondary objective was added late in the study: to calculate estimates of doses that study participants received from the Nevada Test Site.

A.2. History of the HEDR Project

In 1987 the U.S. Department of Energy directed Battelle's Pacific Northwest Laboratories to conduct the HEDR Project, following the 1986 recommendation of the Hanford Health Effects Review Panel (25). In 1988 a Technical Steering Panel was selected to direct the HEDR project. One of the main objectives of the HEDR Project was to evaluate the feasibility of developing a system to estimate individual radiation doses to the thyroid from Hanford's ^{131}I and if feasibility was demonstrated, to develop such a system. The evaluation of feasibility, often referred to as HEDR Phase I, was completed in 1991. It was concluded that the available data regarding source terms, atmospheric conditions, deposition rates, and environmental and food chain transport were adequate to support the development of a system to estimate radiation doses. It was also concluded that existing models and computer codes could be adapted for estimating doses and analyzing the uncertainty of the estimates. As part of the demonstration of feasibility, a preliminary set of dose estimates was calculated for hypothetical representative individuals in a 10-county area around the Hanford site. These were the dose estimates available at the inception of HTDS and during the development of the HTDS protocol.

Based on the Phase I results, the HEDR project proceeded to develop a dosimetry system that included the capability of estimating radiation doses to the thyroid from Hanford's atmospheric releases of ^{131}I. These dose estimates included contributions from dietary pathways, i.e., the consumption of contaminated milk and food products, from inhalation of contaminated air, and from external exposure. In particular these estimates could be calculated for individuals using specific data regarding residence and

dietary history and other factors. One important part of this phase of the HEDR work was establishing the geographical domain within which doses could be calculated. The resulting domain, roughly 250 miles east to west and 300 miles from north to south, was substantially larger than the 10-county Phase I area. A working version of the dosimetry system was in place by early 1994, and the main HEDR final reports were published in April 1994. Thus an essentially final dosimetry system was available in time for use in calculating doses for the HTDS Pilot Study. This was particularly significant to HTDS, since the final HEDR results differed from the HEDR Phase I results in ways that impacted the design of the HTDS Full Study.

In 1999 and 2000, based on recommendations arising from the National Academy of Sciences review of the HTDS draft Final Report (159) and discussion with HTDS investigators, investigators are Battelle Pacific Northwest Laboratories made a number of modifications in the HEDR model's computer program and data files (see Appendix 22). The resulting version of the HEDR system for dose estimation was used to calculate the dose estimates used for the analyses described in this report.

A.3. Special Challenges of Dose Estimation for HTDS

A.3.a. HEDR Dose Models

The central challenge for HTDS arose from the need to complete a version of the questionnaire and program the CATI before the HEDR model was complete. Thus the data items to be included, and the specific definitions of those items, were not completely known. The most difficult areas in this regard were selection of feeding regimes for family cows, delay times before consumption of certain milk products, milk delivery to homes, identification of dairies inconsistent with HEDR information, definitions of leafy vegetables, and the handling of reference diets.

- Cow feeding regimes were undefined when the CATI was first developed. HEDR investigators initially recommended that the interview ask whether the cows were fed fresh grass or green chop. However in the final dosimetry system, cow feeding regimes were defined by whether or not the cows were grazed on irrigated pastureland. Fortunately the CATI included questions about the source of water for the cows, since it was unknown initially whether water would be a significant source of ^{131}I. The information about water source was used to impute whether the pasture was irrigated.

- The final HEDR model did not allow the specification of milk products other than fresh milk and "stored milk." The difficulty with the stored milk component was that it did not distinguish between relatively fresh milk products such as cottage cheese and ice cream, and products with long intervals to consumption such as aged cheese and canned or powdered milk. HTDS collected information only for milk products that were relatively fresh. To allow for the time lag for consumption of milk products, a conversion factor of 0.5 was applied to these products, after consultation with Battelle investigators. Thus the quantity of fresh milk products was multiplied by 0.5 and then added to the amount of fresh milk to obtain the total amount of fresh milk for use as input data by the CIDER program.

- At the recommendation of HEDR investigators, the CATI included questions asking whether commercially produced milk was purchased at a store or delivered to the home. Since milk purchased in a store might sit a few days on the shelf before being purchased, the difference in "holdup times" could affect dose contributions from the fresh milk pathway by about 20-30%. The design specifications for CIDER included definitions of 22 media containing ^{131}I contamination, including milk categories for grocery milk (purchased) and creamery milk (delivered). However in the final version of CIDER the creamery milk category was not implemented. It was therefore necessary to treat milk that CATI respondents described as delivered to their homes as though it was purchased in stores.

- One important challenge facing HEDR was the reconstruction of the commercial milk distribution system within the HEDR geographical domain. When the HTDS CATI was initially designed, HEDR was able to provide a preliminary list of 55 dairies that operated in the Benton, Franklin and Walla Walla counties. These 55 were included in the HTDS interview materials. The final version of the HEDR system included many more dairies. In October 1995 HTDS received from HEDR investigators a list of 163 dairies that were included in the dosimetry system. Occasionally, of course, CATI respondents identified as a milk source a dairy that was inconsistent with the HEDR data, i.e., that did not serve the area in question at the time in question according to the HEDR data. In 12 instances such inconsistencies were observed in the data from 2 or more CATI respondents. In eight of these 12, the dairy in question was mentioned by only 2 CATI respondents. Information about these inconsistencies was sent to the HEDR Task Completion Working Group and to former HEDR investigators in April 1996. Since the reported discrepancies did not provide definitive evidence of inadequacies in the HEDR commercial milk distribution model, that model was not revised in response to these discrepancies. Therefore HTDS adopted the following approach. Whenever a CATI respondent indicated that the participant consumed milk or milk products from a dairy that did not, according to the HEDR data, serve the area in question during the period in question, the dairy was assumed to be unknown for the participant's dose calculation. This had the effect of assigning the HEDR location- and time-specific default as the source of commercial milk and milk products. If the HEDR model specified that only a single dairy served the location at that time, then that dairy was assumed to be the source of dairy products. If the HEDR model identified two or more dairies that served a region during the time period of interest, then the default was defined as a mixture of milk and milk products from those dairies.

- The definitions of "leafy vegetables" differed somewhat between the HTDS CATI and the HEDR dosimetry system. For example the final HEDR definition of leafy vegetables included string beans, while the HTDS definition did not. Another problem with leafy greens was conversion of servings (the unit used in the CATI) to kilograms (the unit required for input into the CIDER program). The HEDR system did not define how this conversion should be calculated. Therefore, after conferring with HEDR investigators and dieticians, HTDS developed conversion factors based on the weights of servings of individual leafy vegetables.

- Reference diets were built into the HEDR dosimetry system to provide default information about dietary factors. Such default information could be used when all or only part of a participant's dietary history was unknown. In HTDS this occurred whenever the CATI respondent was unable to provide the specific information. The Expanded In-Person Interview given to HTDS participants without CATI respondents included no questions regarding quantities of milk and food products consumed during childhood. Therefore the calculation of dose estimates for those with dosimetry data from the Expanded In-Person was necessarily based entirely on default dietary data. The final HEDR system was limited to a total of four sets of reference diets, each containing 120 combinations of age, sex, lifestyle and season for each of nine categories of food and milk products. The reference diets are defined for four different circumstances: milk from backyard cows, milk from commercial sources, goat milk only and cows fed stored feed only. Nearly every HTDS case fell into one of the first two categories (backyard cow's milk or commercial milk). However the HEDR model did not include reference diets for people who were reported to have consumed unknown quantities of both commercial and family cow's milk. Also the CIDER program allowed for the specification of only a single reference diet in each set of input data. Therefore it was impractical to allow a participant's reference diet category to change over time, and HTDS used the backyard cow's milk reference diet for dose estimation.

A.3.b. Technical Issues

When HTDS began, it was clear that the dosimetry data would be complex, and it was therefore unclear whether a CATI would be feasible. In 1990, the fastest PC had a 386 chip and many on the HTDS

staff were still using 286 IBM-AT computers. The complexity of the data implied that a relational or hierarchical data base structure would be required. Three candidate database management systems were given the most serious consideration. The first, SIR (Scientific Information Retrieval) was originally developed on mainframe computers, but had become available for desktop personal computers. SIR is a hierarchical database that allows more than one record per case all indexed by an ID number. However SIR was relatively inflexible and had very poor data entry features to make it unsuitable for CATI. Two relational database management systems, ORACLE and INGRES, originally developed for mainframe environments, were also available on personal computers. Of these two, INGRES was selected on the basis of its flexibility, superior data entry capabilities, substantially lower cost, availability of a local office with technical support, and ability to run on relatively modest personal computers. The flexibility, stability and features of INGRES allowed it to meet all of the study's needs. A copy of the SIR product was also required by the study for use in processing dosimetry data through several steps required to create input files for the CIDER program.

Flexibility of the dosimetry data base management system was important since the CATI was modified several times after data collection began. Moreover the INGRES-based system allowed the capability for interviewers to revise responses in real time during the CATI. Designing the system to permit interviewers to return to and modify previous responses during the interview presented many challenges. However it was considered important since it would minimize the need to temporarily discontinue interviews to permit entry of revisions that would impact the appropriateness of subsequent questions. Since the CATI was expected to be a significant imposition on the time and altruism of the respondent, every effort was made to minimize the number of temporary discontinuations.

The ability to correct data after the interview was also an essential component of the dosimetry data base management system. A separate set of data entry programs were written exclusively for data correction. Initially, the Systems Analyst was the only person allowed to make data corrections. After about one year much of this responsibility was shifted to the CATI Interviewers, who by then had enough experience with the data to make many kinds of corrections, and to judge when a correction was so complex or unclear that it had to be performed by the Systems Analyst. In such instances the Interviewer completed a data correction form and the Systems Analyst made the corrections.

A.3.c. Logistics

HTDS had three computers available for CATIs, each with its own copy of the CATI database. Each CATI database contained only data from the interviews conducted on that computer. After the CATI was completed and any necessary corrections made to the data, the Interviewer copied the data to the local area network maintained by the Epidemiology Program of the Fred Hutchinson Cancer Research Center. Data from the three CATI databases were then captured from the network and combined into a single database on the Systems Analyst's computer.

Creating scenario files (i.e., input data files required by the HEDR dosimetry system) from the CATI databases was a complex process performed by the Systems Analyst. It involved merging records for 18 components of the participant's diet that could vary independently over time into a single set of sequential records. Each diet component existed as a separate table in the INGRES CATI database. They were combined into a single table in the SIR database using INGRES's report writer, programs written in FORTRAN, and the SIR programming language. These were then merged with data regarding the participant's residence history, birth date, and mother's diet if necessary to create the scenario file using a FORTRAN program. For participants whose doses were based on data from the Expanded In-Person Interview, the procedure for creating scenario files was similar but somewhat simpler, because that interview did not collect information about quantities of food and milk products consumed by the participant.

B. Dose Estimation Procedures

When the HTDS protocol was developed in 1993, plans regarding the methods for calculating doses to the thyroid from Hanford's atmospheric releases of ^{131}I could not be specified, since relatively little was known about the dosimetry system that would be available. It was assumed that a dosimetry system would be available, and that it would be capable of calculating doses for HTDS participants using the data collected in the CATI or Expanded In-Person Interview. It was highly likely, though not certain, that dose calculations would be performed by some agency other than HTDS.

B.1. Staffing and Logistics

The study's Systems Analyst/Programmer had primary responsibility for the calculation and management of dose estimates. This included the following tasks: developing procedures for capturing and processing CATI and Expanded Interview data into a format suitable for dose calculations (scenario files), transferring data to the custodian of the dosimetry system to have the calculations performed, receiving the dose estimates back from the custodian of the dosimetry, and making the dose estimate data available to HTDS investigators for statistical analysis.

The HEDR model originally used by HTDS for was installed on a Sun workstation administered by the CDC in Atlanta. Scenario files were created in Seattle and transmitted to Atlanta via the Internet. This version of the model was used to calculate doses used in the analyses for draft HTDS Final Report.

Scenario files typically contained data for between 40 and 45 participants, and the Sun installation of CIDER typically required about 70 minutes to calculate doses for those participants. After the doses were calculated by CIDER, HTDS transmitted the results to Seattle, again via the Internet. CIDER computed 100 realizations of dose for each year from 1944 to 1957 (14 years), and for each of the 10 pathways (inhalation, external exposure, and ingestion pathways for eight food and milk categories). This resulted in at least 14,000 realizations of dose for each participant. If the participant moved during a year, 100 realizations for each of the 10 pathways were computed for each location during the year. HTDS wrote a program to combine the 14,000 realizations into 100 realizations of total dose.

B.2. Revisions of the HEDR Model and Computer Programs

The HEDR model, and more specifically the CIDER program, were revised a number of times during the course of HTDS. A number of HTDS suggestions were incorporated in the final version of CIDER:

1. The maximum number of sources of fresh milk was increased from 3 to 5. Many households had multiple sources of milk such as a backyard cow, commercial milk delivered to the home or purchased at a store, and milk served at school.

2. Goat's milk was retained in the final HEDR model. HEDR investigators considered dropping goat's milk, however HTDS CATI data showed that about 1 % of households drank goat's milk.

3. Cow feeding regime #4 (cow fed mostly stored feed) was retained in the final HEDR model. CATI data showed there were cows fed entirely with hay and stored feed.

4. The maximum number of diet specifications was increased (to 860). This was necessary to accommodate the multiple changes in diet that were typical of HTDS participants. HEDR initially set this limit much lower, based on an assumption that many individuals would share common diets. Even with this increased limit, however, only 40-45 CATI cases could be processed at one time.

5. In the summer of 1997 HTDS detected an error in how the CIDER program handled breast-feeding of participants and helped identify and test the correction

In response to suggestions made in the National Research Council's (NRC's) review of the draft Final Report of the HTDS (159), a number of further revisions were made in the CIDER program by investigators at Battelle Pacific Northwest Laboratories. These are described in detail in Appendix 22, which reproduces a letter report produced by investigators at Battelle Pacific Northwest Laboratories (160). One of the most important revisions was to provide HTDS a version of the CIDER program and the related data libraries that could be run on a desktop personal computer with relatively modest memory (see section 7.1 of Appendix 22). This eliminated the need for a cumbersome procedure described above for passing scenario files and dose estimation output between the HTDS offices in Seattle and the CDC in Atlanta. The HEDR model used by HTDS to estimate the doses used in this report was run on an IBM compatible PC located in the HTDS office. The doses were calculated by the HTDS programmer in much the same manner as described above, although the time CIDER typically required to calculate doses for 40-45 participants decreased to about 7 minutes.

The Battelle investigators made two other significant revisions in the CIDER program. As described in section 7.2 of Appendix 22, the handling of uncertainty in dose conversion factors (DCFs) was revised. The HEDR model accounted for these uncertainties by generating 100 realizations of each age- and sex-specific DCF according to defined uncertainty distributions (161). In the original implementation of CIDER, the order of these realizations was fixed. That is, for every participant, the first dose realization was calculated using the first realizations of the DCFs, the second dose using the second DCF realizations, and so on. This created an artificial correlation between dose estimates of different participants, since they all shared common values of the DCFs in each realization. The revised version of CIDER therefore included an option to randomly permute the order in which the 100 DCFs are selected for each participant, thereby eliminating the artificial correlation. This option was employed for all dose estimates used in the analyses described in this report.

The second significant revision in the CIDER program provided options to assign uncertainties to participant-specific dietary consumption data obtained from CATIs (see section 7.3 of Appendix 22). In the original implementation of CIDER, quantities of food and milk products consumed by a person were treated as uncertain only if they were specified as unknown in the scenario file of input data. If the amount of a food or milk product that a person consumed could be specified in a scenario file, then CIDER treated that amount as fixed, with no uncertainty, in estimating the resulting dose. For most HTDS participants with doses based on CATI data, age-specific quantities of foods, milk, and milk products consumed were reported by the CATI respondent. While it was recognized from the beginning of HTDS that it is unrealistic to ignore the uncertainties in dietary data collected from interviews several decades after the exposure period of interest, the original version of the CIDER program provided no practical means to incorporate that uncertainty. The final version of CIDER includes options to assign uncertainties to reported dietary intakes. These options are described in detail in section 7.3 of Appendix 22

The final version of CIDER and the related data libraries included two other revisions that had only limited impact on the dose estimates. These included correction of source terms beginning August 1951 (see section 3.1 of Appendix 22), and of the uncertainty distribution of fetal dose conversion factors (section 6 of Appendix 22).

C. Doses from the Nevada Test Site

Information released by the U.S. National Cancer Institute (NCI) shortly before and during October, 1997, indicated that persons living in the contiguous 48 states during the 1950s and 1960s were exposed to various levels of ^{131}I released from the Nevada Test Site (NTS). The material released by NCI included estimates of dose for various representative individuals for all counties in the 48 states, as well as more detailed data regarding estimated dose by shot (i.e., by individual test detonation), county, and age. Limited preliminary comparisons for HTDS participants suggested that in many cases the reported NTS

dose estimates were comparable to or even greater than the estimated Hanford doses. Therefore it was judged necessary to add exposure to ^{131}I from the NTS to the list of potential confounding factors.

The CATI and In-Person Interviews included complete residence histories for all participants for the period from December 1944 through 1957. For periods when a participant lived outside the HEDR geographical domain, the county and state of residence were recorded, although details regarding diet and sources of food and milk were not obtained. This was fortuitous, since it provided a means to calculate estimates of NTS-derived dose. Using data regarding representative doses by age and county available from the NCI's website, the HTDS Systems Analyst/Programmer created a program that calculated estimated NTS doses for study participants, based on their residence histories through 1957.

VII. SPECIAL CONSIDERATIONS

A. Assessment of the Feasibility of a Health Study in Native American Populations

A.1. Background

Nine Native American tribes and nations have reservations and ceded lands in the region around Hanford: Colville, Couer d'Alene, Kalispell, Kootenai, Nez Perce, Spokane, Umatilla, Warm Springs, and Yakama. Members of these tribes and nations were exposed to ^{131}I from Hanford, and the original Congressional mandate that led to the HTDS called specifically for the inclusion of "Indian tribes and tribal organizations."

The approach taken in the HTDS regarding the Native American communities was determined by two important characteristics of those populations. First, the lifestyles of many Native Americans were quite different in many respects from those of the non-Native population. In particular, many Native Americans followed traditional cultural practices, especially regarding diet and sources of foods, which might influence the doses they received from Hanford's ^{131}I but which were not explicitly modeled in the HEDR calculational programs. Moreover, many Native Americans maintained a seasonal migratory pattern of residence. Second, because the tribes and nations have sovereign rights recognized by the United States, conduct of a research project such as HTDS would require the approval of each tribal government and active cooperation of tribal members to obtain culturally sensitive data.

As stated in the HTDS protocol (1), the objective of the HTDS with respect to the Native American populations was to assess the feasibility of conducting a study to determine whether thyroid disease was increased among Native Americans exposed to ^{131}I from Hanford. The approach taken to meet this objective involved the following steps:

1. Identifying study designs that could meet the main objective, i.e., to determine whether thyroid disease has increased among Native Americans exposed to ^{131}I from Hanford.

2. Establishing guidelines for assessing whether any of the proposed designs had adequate probability of providing a definitive conclusion regarding the main objective. These guidelines were to be established in collaboration with CDC staff and representatives of the tribes involved.

3. Analyzing demographic data and estimates of thyroid doses from ^{131}I, using dietary and lifestyle information provided by the tribes, in relation to the established guidelines to reach a conclusion about feasibility of a study in the Native American population.

These activities were undertaken in parallel with those of the Full Study. The sections below briefly describe the progression of this component of the HTDS. Demographic data and information about lifestyle practices collected by each tribe, as well as radiation dose estimates specific to each tribe, are considered proprietary and belong to the tribes. These data were made available to the HTDS investigators for purposes of assessing the feasibility of a study in the Native American population with the understanding that they would not be disclosed. Therefore, no data specific to individual tribes are included in this report.

A.2. Initially Recommended Study Design and Guidelines for Assessing Feasibility

Since the main objective of a study in the Native American population is the same as that for the HTDS Full Study, the choice of possible study designs was subject to the same constraints as the HTDS Full Study (see section IV.A.1 above for a discussion of study design considerations). Therefore, the

HTDS investigators initially recommended that a retrospective cohort design using individual dose estimates, similar to that used for the HTDS Full Study, would be most appropriate for a study in the Native American population.

To begin the feasibility assessment of conducting such a study, it was necessary first to obtain information from each tribe about the number of persons who might be available and willing to participate in a study. It was necessary to obtain information to estimate thyroid radiation doses that members of the tribe would have likely received from Hanford. When the HTDS was initiated, work was already underway in conjunction with the Hanford Environmental Dose Reconstruction Project to begin to collect such information within the tribes. A working group was formed to facilitate this effort, and to provide technical assistance. This working group was composed of representatives of each tribe, the Technical Steering Panel of the HEDR project, Battelle, Pacific Northwest Laboratory, the CDC, and the health departments of the states of Washington, Oregon, and Idaho. The HTDS joined this group (the Native American Working or NAWG), and was represented by one of the study investigators at each meeting. This provided a close link between the HTDS and each tribe throughout the entire process of data collection and dose estimation for the Native American population.

As the data collection effort proceeded, it became clear that guidelines for assessing the feasibility of an epidemiologic study should be developed and agreed upon *prior to* examination of any tribal-specific data. At a meeting of the Native American Working Group in January 1994, HTDS investigators proposed the following guidelines for assessing whether an epidemiological study of the recommended (retrospective cohort) design should be conducted in the Native American population.

- Justification of such a study would require pilot data indicating the feasibility of identifying and recruiting adequate numbers of people with a range of radiation doses sufficient to ensure that a one-sided test at the 5% critical level has at least 80% power to detect a linear dose-response for the probability of thyroid neoplasia with a slope of 10^{-5} per mGy.

- If pilot data indicated that such a study would have substantially less power, e.g., below 70%, to detect an effect of this magnitude, then a study in the Native American population would not be recommended on scientific grounds.

This criterion was analogous to that initially proposed for the decision about whether to proceed with the HTDS Full Study. In particular, the target of 80% power to detect an effect of 10^{-5} per mGy was considered scientifically sound, providing a sufficiently high level of statistical power (80%) to detect a relatively small effect (10^{-5} per mGy). It was also considered achievable, based on the dose data available at the time, i.e., the HEDR Phase I dose results.

As a result of the HTDS presentation at the January 1994 meeting, the NAWG formed a Subcommittee on HTDS Study Design to further evaluate the proposed guidelines. In May 1994, this Subcommittee of the NAWG requested the HTDS investigators provide a document regarding possible study designs that might be considered for a thyroid study in the Native American population. In June 1994 the requested document was submitted to the Subcommittee. In that document, the HTDS investigators concluded that, given the objective of determining conclusively whether thyroid disease was increased among Native Americans exposed to Hanford's ^{131}I, the most appropriate study design remained a retrospective cohort study with individual dose estimates, similar to that of the HTDS Full Study.

A.3. Modified Guidelines for Assessing Feasibility

When the essentially final HEDR results became available in April 1994 (27,152), it was apparent that the range of dose estimates for HTDS participants would be substantially smaller than the HEDR Phase I results had suggested. Consequently, the preferred criterion of having 80% power to detect an effect of 10^{-5} per mGy no longer appeared achievable. Therefore, modification of the recommended

criterion had to be considered to ensure adequate power (at least 80%) to detect a dose-response effect of 5×10^{-5}/mGy for thyroid neoplasia. Although this represents a substantial decrease in the power of the study, it was still considered scientifically justifiable (see section V.A.5 above). For example, based on projected baseline probabilities for thyroid neoplasia of 5% and 2% for women and men, respectively, in the HTDS cohort, an effect of 5×10^{-5}/mGy corresponds to doubling the probability for women at a dose of 1000 mGy, and to approximately tripling the risk for men at that dose. This is roughly the magnitude of effect seen in the study of persons in Utah exposed to fallout from the Nevada Test Site (67).

At an October 1994 meeting of the NAWG, representatives of the tribes and nations agreed to provide demographic information and representative dose estimates that were calculated for them by staff at Battelle Pacific Northwest Laboratory as part of the Phase I Native American component of the HEDR project. From 1994 through early 1996, six tribes provided the estimated dose data to HTDS. Five of these tribes also provided information about their numbers of members during the 1940s and 1950s. Based on these data, HTDS investigators calculated predictions of the dose distributions, cohort sizes, and statistical power that might be available for a study in the Native American population.

In May 1996, at a meeting of the Intertribal Council on Hanford Health Projects or ICHHP (which had by then taken the place of the NAWG), HTDS investigators made a presentation regarding the impact of the final HEDR results. For the reasons discussed above, they recommended that the guidelines for assessing feasibility be relaxed. They also presented the results of the power calculations based on the preliminary dose data that had been provided by six tribes or nations. These calculations showed that the projected range of doses and cohort sizes were not large enough to meet the modified guideline of 80% power to detect an effect of 5×10^{-5}/mGy for thyroid neoplasia. However it was also recognized that the dose data available at that time were quite limited with respect to both the number of interviews conducted with tribal members, and the number of tribes completing data collection. Thus, these data would not likely provide sufficiently accurate projections of the dose distributions that would actually be obtained if a Native American study were performed. Consequently, the HTDS investigators recommended that the final determination regarding feasibility of a study be postponed until the second stage of data collection and dose calculation for the tribes was complete.

A.4. Final Assessment of Feasibility

The second stage of data collection took place during 1996 and 1997. One tribe did not complete this stage of data collection and dose estimation. This data collection was intended to provide input data for the calculation of estimated doses for hypothetical representative persons based on realistic assumptions about diet, food sources, and seasonal changes in residence. In 1997 and 1998 CDC staff communicated with each tribe or nation to obtain approval of the assumptions used for calculation of these representative dose estimates. Between late 1997 and mid 1998, CDC and HTDS staff calculated representative dose estimates as data and approvals became available from the tribes.

Dose estimates for each tribe were calculated using several scenarios for the hypothetical representative persons. These scenarios were defined by the following factors:

- Sex.
- Year of birth, including at least 1940, 1942, 1944, 1945, 1946 for every tribe. For three of the tribes, earlier and later birth years were also included. The date of birth was assumed to be January 1 in each year.
- Age at weaning, including at least 0 months (indicating absence of breast-feeding) and 12 months. Older ages at weaning were included for the calculations of some tribes.
- Diet, traditional diet as reported by the tribe versus reference diet as provided by the CIDER program.

Examination of the representative Native American doses revealed that the pattern of estimated dose in relation to birth year was generally the same as that of the individual dose estimates of the HTDS Full Study. That is, estimated doses tended to be highest for representative persons born in 1945. The representative doses decreased with decreasing (earlier) birth year, and were also lower for the 1946 births. One tribe's dose estimates differed slightly from this pattern in that the highest representative dose estimate was for a 1944 birth. However doses for 1945 were similar to those for 1944, and doses still decreased as one moved away from 1944 or 1945, toward either earlier or later birth years.

These representative dose estimates were used to perform statistical power calculations in essentially the same way as those presented by HTDS investigators to the May, 1996, meeting of the ICHHP. Note that the new power calculations differed from the earlier calculations in the following respects: 1) they were based on the representative dose estimates calculated in 1997 and 1998 and based on presumably more accurate scenarios for tribe-specific dietary data and residence histories, and 2) they were based on eight of the nine tribes, rather than the six tribes in the earlier calculations (five tribes provided data for both sets of power calculations).

The statistical power of a study depends in part on the mean and variance of the distribution of doses that would be estimated for the study participants (see Appendix H in HTDS Protocol [1]). These quantities were estimated by 1) estimating the mean and variance of the dose distributions and number of participants for birth year cohorts within each tribe, and then 2) calculating the mean and variance of the overall dose distribution that would result.

To assess the feasibility of a study in the Native American population, initial calculations of statistical power were performed using nonconservative assumptions, i.e. assumptions that would tend to produce an overestimate of the statistical power. This was done as a scoping calculation: if the overestimated statistical power was too low to justify conduct of a study, then the even lower projections of power that would result from using more realistic assumptions would also be evidence against feasibility. If, on the other hand, the initial scoping calculations indicated that adequate statistical power might be obtained, then more careful evaluation of the projected statistical power would be pursued. The non-conservative assumptions that were made for the initial scoping calculations were as follows.

Assumption 1. The projected mean of the dose distribution was calculated by assuming that, within each tribe, the mean dose that would be obtained for each of the 1940, 1942, 1944, 1945, and 1946 birth cohorts would equal the maximum representative dose calculated for that tribe and birth year.

Assumption 2. For each tribe's 1941 and 1943 birth cohorts, for which representative doses were not calculated, the mean was assumed to equal the maximum representative dose calculated for that tribe's 1942 and 1944 birth years, respectively.

Assumption 3. All nine tribes and nations would participate in a proposed study of the Native American population, even though one tribe did not participate in the second stage of data collection and representative dose calculation. Since representative dose estimates were not available for this tribe, it was assumed that each of its birth cohorts would have the same mean dose as the tribe with the highest representative dose estimates. This assumption is quite non-conservative, since the mean doses for this tribe would almost certainly be much smaller.

Assumption 4. For each birth year cohort within each tribe, the variance (V) of the doses was assumed to equal the square of the mean dose (M),

$$V = M^2.$$

The representative dose calculations provided estimated doses for certain types of individuals, but did not provide estimates of the variance that might be observed in a population of real individuals. Therefore, the relationship between mean and variance of doses for populations of real individuals was estimated from the individual dose data available from the HTDS Full Study. The 3191 living evaluable

in-area participants in the Full Study were divided into 100 subgroups defined by sex, year of birth, and geostratum, and the mean and variance of the dose estimates for each subgroup were calculated. Regression analyses indicated that the relationship between variance and mean was approximately of the form

$$V = M^B.$$

For dose estimates which used individual residence histories, individual information collected by the CATI, and HEDR default values for items for which CATI data were not available or for individuals without a CATI, the exponent B was estimated to be 1.8 ± 0.03 (S.E.). For dose estimates which used individual residence histories and HEDR default values exclusively (i.e., no individual CATI data), the exponent B was estimated to be 1.7 ± 0.03. Using an exponent of 2 results in larger estimates of variance, and therefore higher projections of statistical power, than would be obtained with 1.7 or 1.8.

Assumption 5 Non-conservative assumptions were made regarding the numbers of participants who would be available from the nine Native American populations. In particular, for tribes that provided detailed demographic data, it was assumed that all members of the included birth cohorts would be living evaluable participants. For all other tribes it was assumed that a total of 1000 living evaluable participants would be available. This constitutes perhaps quite an overestimate of the number of participants, given the relatively small size of several of the tribes.

Based on these assumptions, sample sizes and dose distributions for a Native American study based on the 1940 – 1946 birth year cohorts for all nine tribes were projected, and the resulting statistical power was calculated. For the initial scoping calculations, a sample size of 6426 living evaluable participants was projected. For thyroid neoplasia, assuming the same background rates as were assumed for the planning of the Full Study, i.e., 5% for women and 2% for men, there would be only 50% power to detect a dose-response effect of 5×10^{-5}/mGy.

In addition to sample size and the mean and variance of the dose distribution, power is also influenced by the baseline probabilities of disease. In particular, all other factors being equal, power increases as the baseline probabilities decrease. Therefore, the sensitivity of the estimated power to the assumed background rates was investigated as part of the initial scoping calculations. To provide a rather extreme boundary for estimated power, calculations were repeated assuming that the baseline probabilities of thyroid neoplasia in the Native American population are only *half* of those assumed for the Full Study (2.5% rather than 5% for women, 1% rather than 2% for men). Under this assumption there would still be power of only 71% to detect an effect of 5×10^{-5}/mGy. Unfortunately, there are no good estimates available of the baseline prevalence of thyroid neoplasia among the nine tribes in the Hanford region. Thus, the assumption of one half used above is intended only to provide a wide boundary of what might be achieved in study power. It is not based on specific estimates of disease prevalence in the Native American population.

In summary, initial sample size and power calculations were carried out based on data provided by eight of the nine tribes under consideration. It is presumed that these data reflect lifestyle patterns and practices specific to each tribe, and that therefore the representative dose estimates more accurately approximate the dose members of each tribe would have likely received from Hanford than earlier estimates. Similarly, it is presumed the demographic data provide a reasonably accurate estimate of the size and demographic makeup of each tribe around the time of the Hanford releases. The five assumptions described above that form the basis for the scoping calculations are deliberately non-conservative. Within a reasonable framework, they are intended to err in the direction of overestimating possible doses, variance of doses, numbers of available participants, and members of participating tribes. Even under such extreme assumptions, a study nearly double in size as the HTDS Full Study (6426 living evaluable participants) would have only 50% power to detect an effect of the magnitude considered scientifically sound. Even under the more extreme assumption that the baseline probabilities for thyroid neoplasia are only half of

those assumed in the Full Study, a study of 6426 living evaluable participants would only have 71% power to detect the same magnitude of effect.

Based on these results, the HTDS investigators recommended that it was not feasible, nor scientifically justified, to undertake a study of the same design as the Full Study (i.e., a retrospective cohort study). Such a study would require more than 6400 living evaluable Native American participants, and would have at most 50% power to detect a dose-response effect of $5x10^{-5}$/mGy for thyroid neoplasia.

B. Coordination with the Advisory Committee

In June of 1990, an Advisory Committee was appointed by the Secretary of the Department of Health and Human Services to advise and consult with the CDC regarding the design and conduct of the study. The committee was established pursuant to the *Federal Advisory Committee Act, 5 U.S.C. (Appendix 2)*. The role of the committee was to review the development of the study protocol and conduct of the Pilot Study, assist in determining the feasibility and design of a full-scale epidemiologic study, and advise the CDC on the analysis of the study data.

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The committee was to be made up of seven scientific and lay members representing different areas of expertise or knowledge. The original members appointed to the committee were: 1) Mr. Lou Stone, representing Native Americans; 2) Dr. Owen Hoffman, Ph.D., representing expertise in Radiation Science; 3) Dr. Genevieve Matanowski, M.D., Dr. P.H., representing expertise in Epidemiology; 4) Mr. Jim Thomas of the Hanford Education Action League, representing environmental organizations in the Pacific Northwest; 5) Dr. Arthur Schneider, M.D., representing expertise in thyroid disease; 6) Ms. Christine Holmes, representing the people of Washington State; and 7) Dr. Larry Jecha, M.D., Health Officer for Benton-Franklin Counties, ad hoc member. The first meeting was held in Atlanta, Georgia in March 1991. Dr. Jecha was appointed Chairman by the CDC.

Prior to the first meeting, Ms. Holmes notified the CDC that she would be unable to participate as a member of the committee. Her position was replaced with Ms. Kristine Gebbie, Secretary of Health for the State of Washington. Due to concern that the affected population might not be adequately represented by a state official, the committee requested a consultant position be added to the committee. This would be a non-voting member familiar with the concerns of those who felt their health had been affected by radiation from Hanford. Ms. Pamela Hoefer, R.N., of the Hanford Downwinders Coalition was selected to fill this position. Ms. Hoefer attended meetings from March 1992 to February 1993.

Over the course of the study, several individuals were replaced as their term of service expired, Dr. Maureen Hatch (epidemiology) replaced Dr. Matanowski in August 1995, Dr. Marlene McKetty (dosimetry) replaced Dr. Hoffman in August 1995, and Ms. Elizabeth Ward (State of Washington) replaced Secretary Gebbie in August 1995. Ms. Judith Jurji replaced Ms. Hoefer in October 1993 as a consultant to the Committee representing the Hanford Downwinders Coalition.

Initially, meetings of the committee were to be held on a quarterly basis in Atlanta. In recognition of the interest in the Pacific Northwest in such proceedings, however, the committee asked that at least one meeting per year be held in Washington State. Following completion of the Pilot Study, meeting frequency was reduced to approximately once per year, with the majority of these held in Seattle, Washington.

Meetings of the Advisory Committee were uniformly open to the public. All materials presented to the committee became public record, with copies available for members of the public at the meetings. Time for public comment and questions was allowed in each meeting's agenda. In addition, meetings held in Washington State were usually accompanied by an evening Public Meeting to allow members of the public to attend and ask questions regarding the study.

Each meeting of the Advisory Committee began with an update on the progress of the study since the previous meeting. These presentations included the status of preparations for the field work, or later, the numbers of study participants completing each phase of the study. Updates on the separate work concerning Native American populations were also included. In addition to monitoring ongoing operations, the Committee focused most of its attention on the following items: 1) review and approval of the initial study protocol; 2) review of the Pilot Study Final Report and recommendations to move forward with a Full Study; 3) development of guidelines for assessing the feasibility of a study of Native American populations; 4) review of the Analysis Plan for the Full Study; and 5) review of the Communications Plan for the Full Study.

C. Public Information

An important aspect of this research was the provision of prompt, accurate, and complete information to the public. In this context it was crucial that contacts be established with members of the populations most interested in (and potentially affected by) the work. Interested parties included representatives of the States of Washington, Oregon, and Idaho, the Native American Tribes and Nations in the study areas, and local area residents.

The public information activities of the study were designed to accomplish the following goals:

1. To assure that residents of the region understood the issues that led to the initiation of the study, the purpose and objectives of the study, its basic epidemiologic design, and the time schedule within which it was to be conducted.

2. To provide opportunities for the public to express concerns and comments regarding the design and conduct of the study, and to answer public questions regarding all aspects of the project.

3. To create public interest and support for the study, particularly in ways that might enhance participation by persons selected to be study participants.

4. To assure broad dissemination and proper interpretation of final study results.

Although all members of the Study Management Team fully expected to contribute in an effort to keep the public informed and to answer questions, Dr. Scott Davis assumed primary responsibility for coordinating such activities. An important initial step in the overall approach was to establish contact with counterparts on the TSP responsible for public information activities (the Communications Subcommittee, chaired by Ms. Mary Lou Blazek). Thus, while the HEDR Project was still underway, the two projects coordinated their efforts to keep the public as well as agencies of the states and Native American Tribes and Nations well informed regarding the planning and the progress of the study. This process was greatly facilitated by the fact that one of the HTDS investigators, Dr. Kenneth Kopecky, was also a member of the TSP and served on the Communications Subcommittee.

Throughout the HTDS, and particularly in its early phases, the SMT participated in public meetings held during the bimonthly meetings of the TSP, and contributed to the planning activities of the Communications subcommittee of the TSP. Members of the SMT, or the Project Manager, attended each TSP meeting. In addition, a member of the HTDS staff attended all meetings of the Communications Subcommittee. In an effort to work more extensively with the TSP in the area of providing public information, at least one member of the SMT was present whenever possible at all TSP-sponsored public meetings and workshops. The HTDS also supplied the TSP with a Fact Sheet that was included with TSP fact sheet mailings. This written material was updated periodically as the study progressed.

Several separate approaches were also taken to provide information to the public regarding the HTDS. Initially, the study protocol was made available for public review and comment prior to its

submission to the CDC and the Advisory Committee. In conjunction with this activity, a series of public (town) meetings were held throughout the Northwest to discuss the protocol with the public and to answer specific questions. Similar public meetings were held in conjunction with meetings of the Advisory Committee held in the Pacific Northwest.

In addition to the study Fact Sheet mentioned above, several study brochures were developed and a newsletter describing the progress and status of the study was initiated. A master mailing list, which included the lists previously maintained by the FHCRC, the CDC, and the HEDR Project was assembled to mail the newsletter and brochures to interested individuals.

Finally, study investigators and staff were available to answer questions on a regular basis. A phone line was designated in the Seattle study office for public inquiries, and a toll-free telephone number was established at the Fred Hutchinson Cancer Research Center for the Hanford Thyroid Disease Study. Persons selected as study participants were encouraged to use the toll-free number to contact the study office if they had questions or scheduling conflicts. The toll-free number was also made available to the general public so that anyone with questions or comments could easily contact the study. As access to the World Wide Web via the internet became more common, a web site for the study was established at the FHCRC. All study brochures and newsletters have been available at that site since January 1997, and are updated as appropriate. Links to the FHCRC, Centers for Disease Control and Prevention, and Hanford Health Information Network sites have been established. The HTDS web site can be accessed at http://www.fhcrc.org/science/phs/htds.

VIII. STATISTICAL METHODS

A. General Approach

A.1. Objectives of the Statistical Analysis

The primary objective of the HTDS was to determine whether thyroid disease has been increased among persons exposed to radioactive iodine released from the Hanford Nuclear Site between 1944 and 1957 (see section III above). To meet this overall objective, the statistical analysis had the following three specific objectives:

1. To estimate, and test the statistical significance of, exposure-response relationships between various thyroid disease outcomes (and other outcome and response variables) and measures of exposure (dose) to radioactive iodine from Hanford.
2. To identify and analyze the effects on these dose-response relationships of any confounding or effect-modifying factors.
3. To investigate, to the extent possible, the shapes of any dose-response relationships that are found.

These specific objectives are discussed in more detail in the following three sections.

A.1.a. Estimation and Testing of Dose-Response Relationships

The primary analyses of this study examined dose-response relationships for the following response variables:

1. Thyroid disease outcomes
   - Thyroid cancer
   - Benign thyroid nodule
   - Thyroid neoplasia
   - Any thyroid nodule (benign, malignant, or suspicious for follicular neoplasm)
   - Hypothyroidism
   - Autoimmune thyroiditis (Hashimoto's thyroiditis)
   - Graves disease
   - Autoimmune thyroid disease (i.e., Hashimoto's and/or Graves)
   - Hyperthyroidism
   - Multinodular thyroid gland
   - Simple goiter
   - Other thyroid disease

2. Other outcome variables
   - Hyperparathyroidism
   - Ultrasound-detected abnormalities of the thyroid (thyroid UDAs)

3. Other response variables
   - Thyroid stimulating hormone (TSH)
   - Total thyroxine (T4)
   - Triiodothyronine resin uptake (T3RU)
   - Free thyroxine index (FTI)
   - Anti-thyroid anti-microsomal antibody (AMA) or anti-thyroid peroxidase antibody (anti-TPO)
   - Anti-thyroglobulin antibody (anti-TG)
   - Thyroid mass
   - Serum calcium

The list of thyroid disease outcomes was comprehensive since the objective ("to determine whether thyroid disease is increased ...") included all thyroid diseases. Therefore it included thyroid diseases for which associations with ionizing radiation have been reported in other settings (thyroid cancer, any thyroid nodule, autoimmune thyroiditis, and hypothyroidism (see section II.B above), as well as other diseases for which associations have not been reported. In view of the public concern about possible unanticipated effects of exposure to ^{131}I from Hanford, and of the Congressional mandate that the study address thyroid morbidity, the exposure-outcome relationship was analyzed and reported separately for each of the outcomes listed above. While the various outcomes can be distinguished in terms of the quantity and strength of the existing evidence for association with exposure to ^{131}I, such distinction played no role in determining how or how extensively the various outcomes were analyzed. Similarly, while the outcomes might be distinguished in terms of severity of impact on a person's life, the same level of effort was expended to assess each diagnostic outcome and its relationship to ^{131}I exposure.

In the primary dose-response analyses, the exposure for each individual was represented by the estimated radiation dose to the thyroid from ^{131}I, as calculated using the CIDER program created by the Hanford Environmental Dose Reconstruction Project. CIDER calculates a dose estimate only if the participant resided within the 246-by-306 mile HEDR geographical domain after December 25, 1944 (27). Therefore ad hoc estimates of the thyroid dose were used for study participants for whom CIDER did not produce a dose estimate; see section VIII.C.1.a.3 below for further details.

The primary dose-response analyses for disease outcomes were based on regression models in which the probability of having the outcome of interest varies as a linear function of thyroid dose. In particular, this primary model permitted background probability of the outcome (i.e., the intercept parameter) to depend on sex, but assumed a common regression coefficient (slope) for dose. The regression coefficient can be interpreted as the change in the probability of the disease outcome, per unit change in dose. So, for example, a slope of 0.005 per Gy indicates that the probability increases by 0.005 (i.e., five per thousand or 0.5 percentage points) for each dose increase of 1 Gy and a slope of 0 per Gy indicates that the probability does not change with dose. Estimation of the dose-response relationship was accomplished by estimating the slope of this stratified linear dose-response model. Since the purpose of the study was to determine whether thyroid disease has been increased, significance testing focused on the null hypothesis that the probability of having the outcome of interest does not vary with dose (i.e., that the slope has value zero) and the one-sided alternative hypothesis that the probability increases with increasing dose (i.e., that the slope is greater than zero). Analogous approaches were taken for the other response variables (TSH, etc.). See section VIII.C.2 below for more details.

One problem that arises in using a linear probability model is the following: if the slope is greater than 0 (or less than 0), then for sufficiently large doses the model will yield probabilities greater than 1 (or less than 0), which are not permissible values. This could present a practical problem for disease outcomes with low background rates, since slightly negative slopes might imply disease probabilities less than 0 for doses with the range that occurred among study participants. As discussed further below, other models for the dose-response relationship were examined as alternatives to the linear model. One of these, the logistic model (described in section VIII.C.2), has the practical advantage that the probabilities derived from it are always greater than 0 and less than 1, regardless of the values of the intercepts, regression coefficient or dose. Therefore the logistic model was employed not only as an alternative to the primary linear model, but also for more detailed investigation of the influences of other factors on the radiation dose-response.

A.1.b. Confounding and Effect Modification

The relationship between disease risk and a possible risk factor such as radiation exposure is said to be "confounded" if both the risk of disease and exposure are correlated with some other factor, called a confounding factor or simply a confounder. If the presence of confounding is ignored, an epidemiological study can produce erroneous results. Suppose, for purposes of illustration, that smokers received higher doses from Hanford's ^{131}I than nonsmokers, and that smoking itself increases the risk of thyroid disease.

Finally suppose, also for this example, that disease risk is unrelated to radiation exposure. Then if a study simply examined the relationship between thyroid disease and radiation dose without accounting for smoking, it might erroneously conclude that disease risk is higher among people more heavily exposed to radiation compared to those with less exposure, because the former group included more smokers. Confounding can also cause a study to conclude erroneously that there is no association between an outcome and an exposure that in fact increases risk of the outcome. The potential problem of confounding can be addressed in epidemiological studies by performing analyses that adjust for the effects of possible confounders.

Effect modification occurs when the association between disease risk and the exposure of interest differs according to a third factor, called the "effect modifier." For example, an association between risk of a certain thyroid disease outcome and radiation exposure might occur only among women, but not among men. In that situation, sex would modify the radiation effect.

Identification and analysis of confounding and effect modifying factors was accomplished through the analysis of generalizations of the logistic dose-response models mentioned above. For disease outcomes, these generalizations allowed the background probabilities of the outcome of interest (i.e., the intercept parameters) and/or the regression parameters to vary as functions of factors in the following categories:

- Sex
- Age at first exposure to ^{131}I from Hanford
- Age at HTDS examination
- Ethnicity
- Smoking
- Other radiation exposure to the thyroid (occupational, medical, dental, fallout from the Nevada Test Site)

In addition, the source of each participant's dosimetry data, i.e., the CATI or the Expanded In-Person Interview, was included among the potential confounding or effect modifying factors.

A.1.c. Shape of Dose-Response Relationships

Investigation of the shapes of dose-response relationships was accomplished through the analysis of generalizations of and alternatives to the primary linear dose-response model, including linear-quadratic and logistic models.

A.2. Estimation and Significance Testing

In drawing inferences about dose-response relationships, two general statistical approaches may be considered: estimation and significance testing. These two approaches are largely complementary, each providing useful information that the other does not, and each is needed to meet the study's overall objective. Therefore both approaches were employed in reporting results of the HTDS. Regarding Objective 1, for example, regression coefficients that represented how each response variable listed in section VIII.A.1.a above changes in relationship to the ^{131}I radiation dose to the thyroid were estimated. These estimates included confidence intervals, which serve to characterize how precisely the true values of the coefficients were likely to have been estimated. In addition, however, significance tests were performed. The one-sided p-values produced by these tests indicated the degree to which the study results were inconsistent with, and therefore evidence against, the null hypotheses that the outcomes are not associated with dose. Thus the two approaches together provided estimates of the magnitude of any radiation effects, and measures of the strength of evidence against the null hypotheses of no association.

B. Definitions of Variables

The kinds of data that were collected and the analyses that were performed for the study can be divided into three categories:

1. Process information. This includes descriptive analyses regarding the numbers of persons selected, the success rates of the various steps in locating and recruiting those persons, and in completion of the study's various data collection activities.
2. Characteristics of living evaluable participants. This includes descriptive analyses regarding demographic variables, as well as characteristics used for the calculation of dose estimates, and information about possible occupational and medical exposures to radiation.
3. Analyses of exposures and outcomes. This includes descriptive analyses of the distributions of radiation dose to the thyroid and of frequencies of disease outcomes and other response variables, as well as the inferential analyses of the radiation dose-response relationships, including analyses of dose effect modification and confounding, and of the effect of uncertainty in the dose estimates.

B.1. Process Information

HTDS used computerized tracing and tracking systems to monitor the progress of the 5199 selected persons through the study's various steps of identification and location (tracing), and contacting, recruitment, and study participation (tracking). At the end of data collection, these systems contained information about the outcomes of the various steps for each selected person. This information was used to describe the success rates of the various steps, and to search for possible sources of bias that might affect the estimated dose-response relationships. The following variables were obtained from the tracing and tracking data:

B.1.a. Stratification Factors

Stratification factors included sex, year of birth, and mother's usual place of residence ("geostratum"), as recorded on the selected person's birth certificate. From the tracing, recruiting and interviewing activities of this study, it was noted that the sex or birth year data were incorrect for a small number of selected persons. The resulting corrections were not made in the stratification data (since there was less or no possibility of detecting such errors for persons who were not located or not interviewed); corrected sex and year of birth data were recorded in separate data files. All analyses involving sex and birth year in this report are based on the corrected data, unless specifically indicated otherwise.

B.1.b. Tracing Outcome

At the end of the tracing component of the study, each of the 5199 selected persons was categorized as not located; located, deceased; or located, alive.

B.1.c. Cause of Death

For all selected persons who were found to be deceased when located, or who were located alive but died prior to meeting the criteria that define a living evaluable participant, death certificates were sought, and the causes of death abstracted. The causes were categorized, taking into account the need to identify conditions related to thyroid or parathyroid disease. In addition, the primary cause of death for each deceased cohort member for whom a cause of death was identified was coded using the International Classification of Diseases, 9th Revision (ICD9-CM). For deaths prior to 1979, (when ICD9-CM was implemented) the primary cause of death was also coded to the system in use at that time.

B.1.d. Contacting Outcomes

At the end of the recruiting component of the study, each person who was located alive was categorized as to whether or not he or she could be contacted by telephone call from the HTDS recruiting staff.

B.1.e. Recruiting Outcomes

At the end of the recruiting component of the study, each contacted person was categorized according to the outcome of the recruiting effort, as either agreed to participate, refused to participate, or lost to contact without agreeing or refusing. Those who agreed or refused were also classified according to whether they agreed or refused on the initial recruiting attempt or after recontacting. Those who failed to decide whether or not to participate by the end of the recruiting period or who initially agreed to participate but subsequently withdrew that agreement were counted as having refused.

B.1.f. Dosimetry Data Collection

Data for dose estimation were collected from two sources. The preferred source of data was the Computer Assisted Telephone Interview (CATI); (see section V.D above, and HTDS Protocol, Appendix 1) of one or more persons with direct knowledge of the participant's infancy and childhood and, for participants born after mid-December, 1994, the participant's mother's pregnancy. In some cases, however, no suitable and willing CATI respondent could be identified, or the information from the CATI was judged to be unreliable. In such cases, the dosimetry information was collected from the participant by means of an expanded version of the In-Person Interview (Exp-IPI) conducted during his or her clinic visit. At the end of the CATI and clinic components of the study, each person who agreed to participate was categorized according to: 1) whether or not a CATI was completed; and 2) whether or not an Exp-IPI was performed. Persons for whom a CATI was performed were also categorized according to the relationship of the primary CATI respondent to the subject of the interview: birth mother, adoptive mother, father, sister, brother, aunt, uncle, other relative, or other. In some instances, CATI data were collected but not used for dose estimation, or CATI and Exp-IPI data were combined (e.g., for participants for whom the CATI was judged inadequate). For purposes of analysis, the participants were classified according to the source of their dosimetry data: CATI versus Exp-IPI.

The CATI included information about the Interviewer's assessment of quality of responses. This information was collected at several points during the interview: following sections concerning sources of milk, the mother's milk consumption and dietary history (if applicable, i.e., if the participant was born after December 15, 1944), the participant's milk consumption and dietary history, the mother's medical history, and the participant's medical history; and after completion of the entire interview. At each of these points the Interviewer recorded his or her subjective assessment of the quality of the responses (high, generally reliable, questionable, or unreliable). If the quality was rated unreliable or questionable, the Interviewer also recorded his or her subjective assessment of the main reason (unclear memory of events, uncertain understanding of questions, hurried responses, or other). In addition, following the sections concerning the participant's milk consumption and dietary history and the participant's medical history, the Interviewer recorded his or her subjective assessment of how often explanatory text was repeated (very often, often, not often). At the end of the CATI the Interviewer recorded his or her subjective assessment of the respondent's cooperation (very good, good, fair, poor).

The Exp-IPI included much more limited information about the Interviewer's assessment of interview quality. At the end of the interview, the Interviewer recorded his or her subjective assessments of the respondent's cooperation and the quality of responses (using the categories defined above). In addition, for interviews rated unreliable or questionable, the Interviewer recorded his or her subjective assessment of the main reason for this rating in narrative form. These narrative answers were classified into the categories defined above for the CATI.

B.1.g. Clinic Participation

Each person who agreed to participate was categorized according to whether or not he or she attended a clinic. Participants (i.e., persons who attended a clinic) were also classified according to whether each of the clinical components was completed: In-Person Interview, ultrasound examination, radiologist review of ultrasound examination, blood draw, thyroid function tests, and physical examination of the thyroid. For participants who received the physical examination of the thyroid, the number of examining physicians, one or two, was recorded. In addition, for participants recommended to have a fine needle aspiration, thyroid scan, or other follow-up for diagnosis of thyroid or parathyroid disease, the results of those procedures were also recorded.

B.1.h. Requests for Medical Records or Slides

Each request for medical records or slides was classified according to the type of request: past medical records, past pathology slides, post-clinic medical records, and post-clinic pathology slides. The "post-clinic" requests refer to records or slides that were created after the participant's clinic visit and as a result of an HTDS recommendation for further evaluation. In addition, each request was classified according to outcome: requested materials received versus not received. For each living evaluable participant the number of requests of each of the four types was recorded, along with the corresponding numbers of requests for which materials were received.

B.2. Characteristics of Living Evaluable Participants

B.2.a. Demographic Data

The following demographic variables were obtained from the tracking system and interview results: sex (corrected), year of birth (corrected), age at HTDS examination, race/ethnicity, religious preference.

B.2.b. Residence History

A residence history is a description of the places a person has lived, and of the dates he or she lived at each place. Residence histories for study participants ranged from the very simple (e.g., a single residence throughout the entire period) to the very complex (e.g., dozens of residences during the period). For each living evaluable participant, the number of residences in the HEDR domain and the duration of residence in the HEDR domain during the period of interest (December 1944 through December 1957) were determined from the CATI or Exp-IPI as appropriate. Note that some living evaluable participants who were born and moved away from the domain before December 15, 1944 had no residences within the HEDR geographic domain during the time period of interest. These participants, designated out-of-area participants, were not excluded from the study.

B.2.c. Dosimetric Data

Dosimetric data includes the information (other than residence history) that is used to calculate an individual's estimated dose, such as the consumption levels and sources of milk and food products. Most of the data used for calculating dose estimates has the characteristic of varying over time. Key determinants of the radiation dose to the thyroid, such as sources of food products and quantities consumed, are subject to change at unpredictable points in time and cannot be characterized by single numerical or categorical variables.

For participants with CATIs as the source of dosimetry data, the participant's consumption levels of the following milk and food products were recorded: processed cow's milk, raw cow's milk, the total of processed and raw cow's milk, processed goat's milk, raw goat's milk, the total of processed and raw goat's milk, fresh fruit, fresh green and leafy vegetables, and eggs from free range chickens. The milk consumption values were reported in the units of grams and 8 ounce servings per day; fruit and vegetable consumption were reported in grams per day; and egg consumption was recorded in grams per days and eggs per week (0, 1, 2, 3, 4-6, 7, > 7).

For participants born or breast-fed after December 14, 1944, the CATI included questions about the mother's sources and consumption of milk and other food products. These were used to record the mother's consumption levels of the following for the period from December 15, 1944 until the participant's birth or end of breast-feeding as appropriate: processed cow's milk, raw cow's milk, the total of processed and raw cow's milk, processed goat's milk, raw goat's milk, the total of processed and raw goat's milk, fresh fruit, fresh green and leafy vegetables, and eggs from free range chickens.

For descriptive purposes, consumption data for milk and food products from the CATI was summarized in two ways. The first way was used to show how consumption levels changed with age: each participant's consumption of a particular milk or food product was reported for any of the following dates that fell within the period of interest (December, 1944 through December, 1957): the six-month anniversary of the participant's birth, and each of his or her first through 15th birthdays.

The second summary of consumption data was used to examine how overall milk and milk product consumption levels were correlated with estimated thyroid radiation dose. To calculate each participant's average consumption level, his or her reported total number of 8 oz. servings for a particular type of milk was first calculated by integrating the reported consumption levels over the time periods for which the CATI respondent reported consumption levels of that milk. For example, if a CATI respondent reported that a participant consumed three 8 oz. servings per day over a period of 2 years, the total consumption was $3 \times 2 \times 365 = 2190$ 8 oz. servings for that period. For these calculations participants born in 1946 were assigned milk consumption values of 0 for 1945. Also participants in the 1940-1945 birth strata who never lived inside the HEDR domain during 1945 were assigned consumption levels of 0 for 1945. If the consumption level for a particular type of milk was unknown for any or all of the time period in question (because the CATI respondent could not report the quantity of glasses consumed), the total consumption was considered unknown for these calculations. Two measures of average consumption were calculated. The first, designated "Average No. of 8 oz. servings per day," was obtained by dividing the reported total number of 8 oz. servings for a given time period by the duration of that period in days (e.g., by 365 for average consumption during 1945). The second measure of average consumption, designated "Average No. of 8 oz. servings per in-area day," used a different divisor: the number of days during the period for which (1) the participant lived within the HEDR domain and (2) the level of milk consumption was reported in the participant's CATI. Average consumption levels were calculated for two time periods: (1) 1945, the year in which by far the largest amount of ^{131}I was released from Hanford (see section IV.A.2 above), and (2) the entire period 1944-1957.

B.2.d. Age at Exposure

Age at exposure to ^{131}I may be a particularly important effect-modifying factor: exposure at younger ages may produce a greater increase in risk of subsequent thyroid neoplasia, and perhaps of other outcomes, compared to exposure at older ages. An assumption of such age dependence is built into the NCRP risk estimates for thyroid carcinogenesis induced by exposure to radioiodine (36). However this assumption relies heavily on extrapolation from human studies of other kinds of radiation exposure, and on animal studies. Therefore particular attention was paid to analyzing the effect of age at exposure. Unfortunately, age at exposure was not simply defined for this study, since most participants' exposures to ^{131}I from Hanford occurred over a protracted period of time, and therefore over a range of ages. Therefore age at first exposure was examined as the possible effect-modifying factor.

For calculating age at first exposure to ^{131}I from Hanford, the definition of age was generalized from its usual definition to include negative values representing gestational ages, extending from birth back to gestational age 90 days (about –0.5 years), the age at which thyroid function is assumed to begin in the HEDR model (161). Similarly, the definition of a participant's residence was generalized to include the participant's mother's residence during the participant's gestation from age –0.75 to 0 (birth). With these conventions, age at first exposure was defined as the maximum of –0.75, age on December 15, 1944, and age when the participant first resided in the HEDR geographical domain.

B.2.e. Medical and Dental Radiation Exposure History of Participant

For participants with CATIs as the source of dosimetry data, information about medical and dental radiation exposures was obtained by combining data from the CATI and In-Person Interviews; otherwise the information was obtained from the In-Person Interview alone. For descriptive purposes, each living evaluable participant was classified according to whether or not he or she had a history of each of a number of diagnostic radiation procedures: CAT scan of the upper body, diagnostic x-ray of the head, diagnostic x-ray of the neck, diagnostic x-ray of the chest or upper body (including mammograms), diagnostic x-ray of the stomach or mid-back, barium enema, upper GI, intravenous pyelogram, fluoroscopy of the upper body, thyroid nuclear scan, and other nuclear scan. Participants were also classified according to whether they had a history of the following types of radiation treatment: radiation treatment for any cancer other than thyroid cancer, x-ray treatment to the upper body for acne, x-ray treatment for ringworm, x-ray treatment for enlarged tonsils, x-ray treatment to the upper body for tuberculosis, x-ray treatment for scalp infection, x-ray treatment for enlarged thymus, and x-ray treatment to the upper body for any other reason. Finally, participants were classified according to whether they ever had routine dental x-rays, ever had routine dental x-rays more than once per year, and ever had dental x-rays that did not usually include shielding of the neck area.

B.2.f. Occupational History

The In-Person Interview included questions about employment in a number of industries or occupations that might involve exposure to ionizing radiation. For descriptive purposes, each living evaluable participant was classified according to whether or not he or she had ever worked in each of the following industries and occupations: geology; metallurgy; metal processing; ore refining; mining; nuclear industry; on the premises of a nuclear facility; health care with exposure to radioactive materials or x-rays; scientist, researcher or student with exposure to radioactive materials or x-rays; military working around nuclear testing, nuclear submarines or other radiation exposure; any other industry or occupation that might have caused exposure to radioactive materials or x-rays.

B.2.g. Smoking History

Information about smoking histories was obtained from the In-Person Interview. Participants were categorized according to history of ever smoking each of filtered cigarettes, nonfiltered cigarettes, any cigarettes, cigars, or pipe. In addition, for those who reported ever smoking a particular product, the level of use of that product was quantified in terms of cigarette pack-years (average number of 20-cigarette packs per day times number of years cigarettes smoked), cigar-years (average number of cigars per day times number of years cigars smoked), and pipe-years (average number of bowls per day times number of years pipes smoked) as appropriate.

B.2.h. Exposure to ^{131}I from the Nevada Test Site

Information released by the U.S. National Cancer Institute (NCI) in 1997 (162), indicated that persons living in the contiguous 48 states during the 1950s and 1960s were exposed to various levels of ^{131}I released from the Nevada Test Site (NTS). The information released by NCI included estimates of dose for representative individuals in all counties in the 48 states, as well as more detailed data regarding estimated dose by shot (i.e., by individual test detonation), county, and age. Limited preliminary comparisons for HTDS participants suggested that in many cases the reported NTS dose estimates were comparable to or even greater than the estimated Hanford doses. Therefore it was judged necessary to add exposure to ^{131}I from the NTS to the list of potential confounding factors.

For HTDS, the "estimated NTS dose" was defined as the thyroid dose from ^{131}I entering the atmosphere from tests conducted at NTS between 1951 and 1957, inclusive, as estimated from data made publicly available by NCI. The limitation to tests conducted through 1957 was based on two considerations: 1) although NCI reported exposures through 1972, it was estimated that 99% of the ^{131}I was released from 90 tests conducted between 1952 and 1957, and 2) HTDS collected complete residence histories for all living evaluable participants only through 1957, including residences outside the HEDR domain. Each living evaluable participant's estimated NTS dose was calculated as the total of doses from all 57 shots at the NTS between 1951 and 1957. HTDS staff wrote computer code to accumulate for each participant, the estimated thyroid dose from each shot taking into account the participant's residence history.

B.3. Analyses of Exposures and Outcomes

B.3.a. Exposure Data

The primary analyses of dose-response relationships were based on individual estimates of radiation dose to the thyroid, specifically organ doses to the thyroid which were estimated from the residence history and dosimetric data collected during the CATI and/or Exp-IPI. The participants were divided into two categories regarding dose estimates:

- The first category, and by far the largest, includes the participants who lived at some time between December 15, 1944, and December 31, 1957, in the geographical domain defined by the Hanford Environmental Dose Reconstruction Project. Doses for these participants were calculated using the CIDER program, which was created by the HEDR Project. These are designated **in-area participants**.

- The second category consists of persons who never resided within the HEDR domain between December 15, 1944, and December 31, 1957. The CIDER program does not provide dose estimates for these participants. These are designated **out-of-area participants**.

The dose estimates produced by CIDER for the in-area participants were derived from information collected during the CATI and/or Exp-IPI. After review and editing, these data were formatted into scenario files that served as input to the CIDER program (163). The CIDER output for each in-area participant consisted of 100 realizations of the estimated cumulative total organ dose to the thyroid from ^{131}I, as well as corresponding sets of realizations of dose by year and by pathway. The CATI and Exp-IPI also included a short series of questions meant to elicit the respondent's level of knowledge and opinions regarding thyroid disease, radiation, and Hanford, which were used to investigate the possibility of recall bias.

It is important to recognize that in the CIDER program each of the 100 realizations of dose is calculated for a fixed set of conditions regarding the source term and environmental transport, and that these conditions for a given realization were the same for every participant. The 100 realizations were

obtained by randomly varying the conditions, i.e., the uncertain parameters in the HEDR models for source term, transport, etc., in order to characterize the uncertainty in the resulting dose estimates (25). Thus it is useful to view each realization as consisting of a set of doses, one for each in-area participant. This can be illustrated by the following table, in which the k-th realization of dose for the i-th participant (i = 1, …, N) is denoted $D_{i,k}$, where N is the number of living evaluable in-area participants.

Table VIII.B-1. Schematic Illustration of Dose Realizations

	Realization			
Participant	1	2	…	100
1	$D_{1,1}$	$D_{1,2}$	…	$D_{1,100}$
2	$D_{2,1}$	$D_{2,2}$	…	$D_{2,100}$
…	…	…	…	…
N	$D_{N,1}$	$D_{N,2}$	…	$D_{N,100}$

Each column in this table, i.e., each realization $\{D_{1,k}, \ldots, D_{N,k}\}$, is a set of doses which are consistent in the sense that they were all calculated under the same conditions. For example, the amounts of ^{131}I released into the air (the "source term") will be higher in some realizations and lower in others. This variability is likely to induce a corresponding variation in dose estimates: realizations with higher or lower source terms may tend to produce higher or lower dose estimates, respectively, for many participants. As a result, the dose estimates of different participants may tend to be correlated across the 100 realizations. Some components of the dosimetry model, for example those subject to the constraint of mass balancing, may introduce negative correlations. Consider the example of atmospheric transport. For each realization to be properly mass-balanced, if one region receives a particularly high deposition of ^{131}I, then the depositions in other regions may tend to be lower. Thus estimated doses of participants exposed largely from the depositions in the first region may tend to be negatively correlated with the doses of those exposed to ^{131}I deposited in other regions.

In the original version of the CIDER program, the dose conversion factors (DCFs), which in effect convert estimated amounts of ^{131}I taken up by the thyroid (measured in Ci) into estimated dose (in mGy or related units), were assumed to be the same for all participants in each realization. This almost certainly induced an unrealistically high level of positive correlation: every participants' dose estimates would tend to rise or fall together as the DCFs increased or decreased from realization to realization. Therefore the CIDER program was modified to permit the realizations of DCFs to be randomly permuted for each participant (see Appendix 22). This was expected to greatly reduce the correlation of dose realizations across participants.

A further revision of the CIDER program allowed uncertainties to be applied to dietary input data for CATI participants. Incorporating this additional source of uncertainty would of course increase the uncertainties of the resulting dose estimates. Since the magnitudes of these uncertainties could not be determined or estimated from the data collected for HTDS or from other sources, the revision of CIDER allowed their magnitudes to be specified (see Appendix 22). As described further below, this capability was used to assess how estimates of radiation dose-response parameters were affected by the incorporation of additional uncertainties of various plausible magnitudes.

For many purposes it was useful to have a single number or "point estimate" to represent each participant's dose. For each in-area participant, the median of the 100 realizations of dose, d_i = median($D_{i,1}, \ldots, D_{i,100}$) for participant i, was used as a summary measure of that participant's dose. In particular, the median doses were used for descriptive purposes that required categorization of participants by dose. Two other point estimates were also calculated for each in-area participant. The first is the geometric mean:

$$GM_i = \exp(N^{-1} \Sigma_k \ln D_{i,k}).$$

Finally, for comparability with reported results of the Utah Thyroid Study (67,92,164), the arithmetic mean dose (called simply the mean dose) was also calculated:

$$M_i = N^{-1} \Sigma_k D_{i,k}.$$

For descriptive purposes, it as also useful to have summary measures of the uncertainty of dose estimates for the in-area participants. For use with the median doses, the ratio of the 95th percentile to the median dose was calculated. In addition, the geometric standard deviation (GSD_i) and standard deviation (SD_i) were calculated for use with the geometric and arithmetic means, respectively:

$$GSD_i = \exp([(N-1)^{-1} \Sigma_k (\ln^2 D_{i,k} - N^{-1} [\Sigma_k \ln D_{i,k}]^2)]^{1/2})$$

$$SDi = [(N-1)^{-1} \Sigma_k (D_{i,k}^2 - N^{-1} [\Sigma_k D_{i,k}]^2)]^{1/2}.$$

Preliminary analysis of doses indicated that the empirical distributions of the logarithms of the individual participant's doses, ln(Di,1), … , ln(Di,100), were roughly normally distributed, with variances that changed relatively little from participant to participant. As a result each participant's median and geometric mean were nearly equal. Thus analyses of dose-response relationships were essentially unchanged whether based on medians or geometric means. Also, the arithmetic mean doses were roughly a constant multiple, C, of the median or geometric mean where C > 1. Preliminary results suggested that the value of C will be about 1.35, i.e., that the mean doses were about 35% larger than the median or geometric mean doses. Since mean doses were expected to be consistently larger than geometric mean or median doses, the estimated effects of exposure on outcomes were expected to be smaller in magnitude if based on mean dose, compared to median or geometric mean dose.

B.3.b. Alternative Representations of Exposure

In addition to the individual estimates of thyroid radiation dose described above, alternative representations of exposure to Hanford's ^{131}I were defined. When the HTDS protocol was developed, the consideration of such alternatives arose from the possibility that the HEDR project, which had not then completed its feasibility phase, might not provide a system for calculating individual dose estimates. Since the HTDS did in fact develop a dosimetry system that could be adapted for HTDS use, this reason for considering alternative characterizations of exposure became moot. Nevertheless, alternative characterizations remained of interest, since they could be used to assess whether there might be evidence of a radiation effect that was not revealed in the primary dose-response analyses using individual dose estimates from the CIDER program. Two alternative representations of exposure were considered: geostratum and a dichotomous (high versus low) exposure variable. Unlike the estimates of thyroid radiation doses, which were available only for the in-area participants, both of these alternative representations of exposure were defined for all living evaluable participants, including the out-of-area group.

B.3.b.1 Geostrata

The first alternative was simply the participants' geostrata, i.e., the nine geographical regions that were defined for the selection of potential study participants (see section IV.A.1 above). The rationale for considering geostratum as an alternative representation of exposure was as follows. The results of the HEDR project strongly suggested that doses received by participants varied markedly according to their places of residence, particularly during the period of highest ^{131}I releases (26). Since each participant's geostratum was his or her mother's usual place of residence at the time of the participant's birth, many participants were likely to have resided in their respective geostrata for at least some of their infancy or

childhood. Therefore geostratum might be at least somewhat correlated with the doses study participants received.

There are obvious limitations in using geostratum as an alternative representation of exposure. Most importantly it fails to account for changes in residence or dietary factors that can strongly influence the dose an individual actually received. Therefore analyses of cumulative incidence of disease outcomes or prevalence of thyroid UDAs in relation to geostrata were unlikely to provide conclusive evidence either for or against an effect of ^{131}I from Hanford.

B.3.b.2. Dichotomous Exposure Variable

The second alternative was defined in such a way as to reduce the weaknesses inherent in using geostratum as a characterization of exposure. Specifically, an attempt was made to assign the living evaluable participants into relatively high and low exposure groups using simple characterizations of the residence and milk consumption histories. The high exposure group was defined to include participants who lived in the downwind counties closest to Hanford during 1945 and consumed appreciable quantities of milk, while the low exposure group was defined to include participants who lived sufficiently far away from Hanford and/or drank sufficiently small quantities of milk. Specifically, the two groups were defined as follows:

- High exposure group. This group included all living evaluable participants born before July 2, 1945, who lived in Benton (excluding the city of Richland, but including Kennewick), Franklin (including Pasco), or Adams County for at least 180 days during 1945, and who were reported to consume an average of at least one 8 oz. serving of milk and milk products per day during 1945. Since this criterion depends in part on the participant's individual milk consumption history, only participants with CATI data used for dose estimation could be included in this group.

- Low exposure group. This group included living evaluable participants in the following categories:

  (i) Out-of area participants.

  (ii) In-area participants born before January 1, 1946 who lived in Ferry, Stevens, or Okanogan County or outside the HEDR domain from December 15, 1944 or their birthdays (whichever occurred first) through December 31, 1951.

  (iii) In-area participants born before January 1, 1946 who lived in Ferry, Stevens, or Okanogan County or outside the HEDR domain from December 15, 1944 or their birthdays (whichever occurred first) through December 31, 1945, and who lived outside Benton, Franklin and Adams Counties from January 1, 1946 through December 31, 1951.

  (iv) In-area participants born before January 1, 1946 who are not in categories (i) or (ii), but who lived outside Benton, Franklin and Adams Counties from December 15, 1944 or their birthdays (whichever occurred first) through December 31, 1951, and who were reported to consume an average of less than one 8 oz. serving of milk and milk products per day during 1945. Note that only participants with CATI data used for dose estimation could meet this criterion.

  (v) In-area participants born after December 31, 1945 who lived outside Benton, Franklin and Adams Counties from birth through December 31, 1951.

While the exposure groups defined above were expected to provide a more reliable characterization of exposure than geostratum, they could not be expected to provide a perfectly accurate separation of high- and low-exposed participants. For example, it could not be assured that every

participant in the high exposure group had a higher dose from Hanford's ^{131}I than every participant in the low exposure group. The criteria above were defined to ensure a reasonable likelihood that the high and low exposure groups consisted largely of participants with comparatively high and low doses, respectively.

The categories defined above did not include all possible circumstances, e.g., participants who lived at least 180 days in Benton, Franklin or Adams Counties during 1945 but who were reported to consume an average of less than one 8 oz. serving of milk and milk products per day during 1945. Living evaluable participants who did not meet any of the criteria above for either the high or low exposure group were not assigned to either group, and were excluded from analyses involving the dichotomous exposure variable.

B.3.c. Outcome Data

The outcome data for this study included the following:

- Diagnoses of thyroid disease and primary hyperparathyroidism
- Presence of ultrasound-detected abnormalities of the thyroid (UDAs)
- Results of thyroid function and antibody tests, thyroid volume, and serum calcium levels

See section VIII.A.1 a. above for a more detailed list of outcomes, and IV.C for definitions of outcomes. Data for the first two categories (diagnoses of thyroid disease and hyperparathyroidism, and ultrasound-detected abnormalities) were obtained from the Final Diagnosis Determination Form (FDDF; Appendix 20). Thyroid mass was obtained from the ultrasound measurements recorded by the HTDS sonographer at the time of the clinical examination (LxWxHx.55 calculated separately for the right and left lobes, then added together), unless revised by the radiologist. Results of thyroid function and antibody tests and serum calcium levels were obtained from reports provided by the laboratories performing the analyses.

One disease outcome category from the FDDF requires special comment: "thyroid nodule suspicious for follicular neoplasm." This category was included on the FDDF to allow for the possibility that diagnostic information would not permit a definitive determination of a nodule's behavior (benign versus malignant). It was also used for participants who, on HTDS cytology review, were described as having a nodule with an intermediate or high probability of being a follicular neoplasm, and who did not have a subsequent surgery that could provide a definitive histologic diagnosis. At the end of the data collection period, all participants remaining in the "suspicious" category were in this latter group. None of these cases were suspicious for papillary carcinoma. Most of the nodules in this group were likely to be benign, however they could not be counted among the confirmed cases of benign nodules. Therefore they were included in the combined category of participants with any thyroid nodule. In addition, they were included along with the benign nodules in a secondary analysis to assess whether their omission might disguise a dose-response.

For each participant with a disease outcome, additional information about that outcome was available from the FDDF, including the basis for the diagnosis and, for some outcomes, possible etiologies or contributing causes (see Appendix 20). Similarly, for participants with a thyroid UDA, the FDDF included further information about the UDA. Therefore it was important to identify a primary definition for each outcome, as well as alternative definitions of outcome that would be considered. The primary definitions were intended to include cases with (1) a broad but meaningful range of specific outcome subtypes (e.g., benign thyroid nodules of any histologic/cytologic type), and (2) an adequately definitive basis for diagnosis (e.g., based on histologic or cytologic evidence confirmed by the HTDS evaluation). The alternative definitions were intended to permit analysis of the effects of (1) restricting outcomes to more specific subtypes (e.g., benign thyroid nodule excluding nonneoplastic disease, or non-iatrogenic hyperthyroidism), and (2) changing the level of diagnostic certainty (e.g., including all diagnoses, ranging

from those based on HTDS evaluation to those based only on participant/respondent report). The primary and alternative definitions of the various disease and ultrasound outcomes are given in section IV.C.

C. Analytic Methods

A variety of descriptive analyses were performed to summarize process information, characteristics of the living evaluable participants, and exposure and outcome data. These analyses made use of standard descriptive statistical techniques, primarily frequency tables and crosstabulations, calculation of estimates of central tendency (e.g., means, medians) and dispersion (e.g., ranges, 5^{th} and 95^{th} percentiles), and simple plots of standard types (e.g., bar plots, pie charts, scatter plots).

C.1. Statistical Models for Analyses of Exposures and Outcomes

Standard statistical techniques were used to provide descriptions of radiation dose estimates and outcomes. These included the calculation of summary statistics (median, minimum, maximum, mean, standard deviation) and cumulative distribution functions to describe distributions of estimated doses, for presentation in tabular or graphical form. Uncertainties of dose estimates for in-area participants were illustrated graphically, including cumulative distribution functions of ratios of the 95th percentile to the median dose, and of geometric standard deviations (GSD) of dose, and scatterplots of the 95th percentile-to-median dose ratio (on the vertical axis) by median dose (horizontal axis, on logarithmic scale), and of GSD by geometric mean dose.

Summaries of outcome data were displayed in tables showing the numbers of cases and relative frequencies for subcategories defined by, e.g., basis for diagnosis or disease subtype, for women and men separately, and for both sexes combined.

The relationships between outcomes and estimated dose were displayed in tables showing numbers of cases within dose categories, for women and men separately and for both sexes combined. The number of cases in each category was also expressed as a percentage of the number of living evaluable participants in the category.

C.1.a. Inferences About Dose-response Relationships: Models for Objective 1

As described in the HTDS Protocol, Appendix H (1), the primary analysis of exposure-outcome relationships for disease outcomes focused on the cumulative incidence of the outcome among living evaluable participants at the time they are examined for the study. "Cumulative incidence" referred specifically to the proportion of participants with the outcome of interest diagnosed at any time up to and including the HTDS examination. Thus it is most comparable to "period prevalence" as defined for the Utah Thyroid Study (92), if it is understood that the beginning of the period of observation is the birth of the participant. However the term "cumulative incidence" was used for HTDS, since "period prevalence" implies a risk period defined by uniform calendar dates for all study participants. One basic model served as the starting point for estimation and significance testing of the dose-response relationships for the disease and ultrasound outcomes listed in paragraph II.B above. This was the stratified linear probability model:

[1] $P_j(d) = A_j + B \times d$

where

j = 1, 2 indexes the strata defined by sex,
d is the cumulative dose to the thyroid,

$P_j(d)$ is the probability that a living evaluable participant in stratum j and with dose d has the disease of interest,
A_j is the background probability for participants in stratum j, i.e., the probability of the outcome in the absence of the radiation exposure, and
B is the regression coefficient that expresses the magnitude of the radiation effect.

Like disease outcomes, the presence or absence of thyroid UDA is also a binary outcome, and model [1] is applicable. However unlike the disease outcomes, for which diagnoses could have occurred any time up to and including the HTDS examination, detection of thyroid UDAs was based entirely on the HTDS examination. Therefore for thyroid UDAs, the probability $P_j(d)$ in model [1] refers to the prevalence, rather than cumulative incidence.

The regression coefficient B in [1] represents the slope of the dose-response. According to the model, the probability of disease increases with increasing dose, does not change with dose, or decreases with increasing dose depending on whether $B > 0$, $B = 0$, or $B < 0$, respectively. Suppose, for example, that the background probability of thyroid cancer among women is $A_1 = 0.007$. Table VIII.C-1 illustrates how the probability of thyroid cancer varies in relation to dose for three different values of the slope B.

Table VIII.C-1. Illustration of Positive, Zero, and Negative Dose-responses

	Probability of Thyroid Cancer for Women ($A_1 = 0.007$)		
Dose (mGy)	B = 0.025 per Gy	B = 0.000 per Gy	B = –0.005 per Gy
0	0.0070	0.0070	0.0070
100	0.0095	0.0070	0.0065
1000	0.0320	0.0070	0.0020

Note that if $B < 0$, then for sufficiently large doses, the probability of disease will be less than or equal to 0, especially for outcomes with low background rates. For example, continuing the illustration from the table above, if B = –0.005 per Gy, then for women with doses greater than 1400 mGy (1.4 Gy) the linear probability model implies that the probability of disease is less than 0, which is impossible. While it is almost certain that probabilities of disease outcomes do not decrease with increasing dose, the estimate of B may be less than 0 due to the essentially random variability of disease occurrence, especially if the true value of B is near 0. Therefore the parameters of model [1] were estimated under the constraint that every participant's probability must be greater than 0. (Estimation was similarly constrained to ensure that every participant's probability is less than 1, the maximum possible value for probabilities. However this constraint was rarely invoked since most outcomes had sufficiently low background rates.)

Since the linear probability model could yield impermissible values for probabilities, e.g., cumulative incidence of disease or thyroid UDA prevalence less than 0 (see section VIII.A.1.a above), the sex-stratified logistic regression model was also considered.

[2] $$P_j(d) = \exp(A_j + B \times d) / [1 + \exp(A_j + B \times d)].$$

It should be noted that the parameters of the logistic model do not correspond directly to those of the linear model [1]. For example, the values of the intercept parameters A_j are not the background probabilities. Nevertheless the background probabilities can be calculated from the parameters of the logistic model:

[3] $$P_j(0) = \exp(A_j) / [1 + \exp(A_j)] \text{ for } j = 1, 2.$$

Although the regression coefficient B in the logistic model does not represent the slope of a linear probability model, it can nevertheless be used in a similar way to assess the evidence for or against the existence of a dose-response relationship.

A stratified model analogous to [1] was used for laboratory values (thyroid function, antibody tests, and serum calcium) and thyroid volume:

[4] $E_j(d) = A_j + B \times d$

where

$E_j(d)$ is the mean of the (possibly transformed) value for living evaluable participants in stratum j and with dose d, and
A_j is the background mean for participants in stratum j, i.e., the mean in the absence of the radiation exposure, and the other terms are defined as for [1].

Transformation of some laboratory values (e.g., to logarithms) was expected to be appropriate since they are bounded below by zero and likely to be right-skewed. Analyses of TSH, T4, T3RU, and FTI in relation to estimated thyroid radiation dose were limited to participants who were not on thyroid hormone replacement at the time of their HTDS examination.

As mentioned above, three different assays were used for TSH, and two assays for anti-thyroid antibody. The three TSH assays (RIA, EIA-1, and EIA-2) all measured the same quantity (serum concentration of TSH). Therefore for TSH model [4] was generalized to assess whether B and/or the A_j differed among the three assays. The situation was different for the two anti-thyroid antibody assays: AMA and anti-TPO do not measure the same quantity. Therefore their data were not combined, and model [4] was fit separately to the AMA and anti-TPO data.

C.1.a.1. Alternative Point Estimates of Dose to Thyroid from Hanford ^{131}I

As noted above, two point estimates of each in-area participant's dose were available in addition to the median: the arithmetic and geometric means. To assess the extent to which the results might be influenced by the choice of the point estimate to represent dose, certain analyses were repeated using the arithmetic and geometric means.

The use of arithmetic mean doses is similar to the approach taken in the analysis of the Utah Thyroid Study (92). However it must be noted that the results of the HTDS and the Utah study are not directly comparable, even for the analyses of neoplastic diseases, since their outcome variables differ: the HTDS dealt with lifetime cumulative incidence through the early-to-mid 1990s, in a cohort born in the early-to-mid 1940s; the Utah study dealt with incidence and prevalence in the late 1960s and mid 1980s, in a cohort born from the mid-1940s to the mid-1950s.

C.1.a.2. Sensitivity of Results to Large Doses

The distribution of doses was expected to be quite skewed, with large numbers of participants having comparatively low doses, and small numbers having quite high doses. Therefore, for the disease outcomes and thyroid UDAs, analyses were performed to assess whether the regression coefficient B might be inordinately influenced by the high dose participants. In particular, two empirical checks were made to assess whether the estimated regression coefficient adequately represents the dose-response relationship over the lower dose range. The first check consisted of fitting a linear-quadratic exposure-response model:

[5] $P_j(d) = A_j + B_1 \times d + B_2 \times d^2$

If the quadratic term B_2 was found to be significantly different from 0, then the estimated regression coefficient B from the linear model [1] could be interpreted as underestimating or overestimating the effect in the low dose range, depending on whether the estimate of B_2 is negative or positive, respectively. The second check consisted of fitting the linear model [1] with participants in high dose categories excluded.

C.1.a.3. Dose Estimates for Out-of-Area Participants

It cannot be assumed that the out-of-area participants were unexposed to ^{131}I from Hanford. Indeed, results of the HTDS Pilot Study suggested that many out-of-area participants lived in locations near the HEDR domain at various times during 1945-1957. Furthermore, results of the HEDR project strongly imply that people living outside the domain could have received doses higher than those for some people who lived inside the domain; see for example, Figures 6 through 8 of Farris, et al. (26). The following empirical approaches were taken to provide dose estimates for the out-of-area participants. These dose estimates were used to assess the sensitivity of dose-response results to assumptions about the doses.

- Out-of-area dose assumption 1: All out-of-area participants were assigned doses of 0 mGy.

- Out-of-area dose assumption 2: Each out-of-area participant who lived anywhere in Washington State, Oregon, Idaho, Montana, British Columbia, or Alberta between December 15, 1944, and December 31, 1957, was assigned the maximum dose for a representative child residing in the grid square of the HEDR domain closest to any of the participant's residences. All other out-of-area participants were assigned doses of 0 mGy.

The assignment of maximum doses required for assumption 2 was accomplished as follows. The region lying outside the HEDR domain but within Washington State, Oregon, Idaho, Montana, British Columbia, or Alberta was divided into four subregions, each corresponding to part of the boundary of the HEDR domain.

- North/northeast subregion: British Columbia, Alberta, and counties in the northern halves of Idaho and Montana, corresponding to the northern boundary and upper half of the eastern boundary of the HEDR domain.

- Southeast subregion: The remaining counties of Montana and counties in Idaho lying north of a boundary defined by county lines extending approximately southeast from the southeastern corner of the HEDR domain, corresponding to the lower half of the boundary of the HEDR domain.

- South subregion: The remaining counties in Idaho, and counties in Oregon lying east of a boundary defined by county lines extending approximately southwest from the southwestern corner of the HEDR domain, corresponding to the southern boundary of the HEDR domain.

- West subregion: The remaining counties in Oregon, and all counties in Washington State, corresponding to the western boundary of the HEDR domain.

The maximum estimated dose for a representative child was then calculated for each of four the segments of the HEDR domain boundary to which the subregions correspond. Based on a representative child born in December 1944 with a diet of backyard cow's milk and produce, the associated doses were 51 mGy for the north/northeast subregion, 12 mGy for the southeast subregion, 14 mGy for the south subregion, and 8 mGy for the west subregion.

The residence histories of the out-of-area living evaluable participants were then reviewed to identify those who had ever lived in any of the four subregions between December 1944 and the end of 1957. Those who had were assigned the highest dose for any subregion in which they had lived during that period.

For each disease and thyroid UDA outcome, the sensitivity of the dose-response results to the inclusion or exclusion of the out-of-area participants was assessed by comparing the results from the primary analysis (which excluded the out-of-area participants) to those obtained from the following two scoping analyses. The linear probability model [1] was used for all of these analyses.

- Scoping Analysis #1: Out-of-area participants were assigned doses under assumption 1 (i.e., extremely low doses) if they did not have the outcome of interest, and under assumption 2 (comparatively high doses) if they did have the outcome of interest, i.e., imposing a strong positive dose-response relationship among the out-of-area participants.
-
- Scoping Analysis #2: Out-of-area participants were assigned doses under assumption 1 (i.e., extremely low doses) if they had the outcome of interest, and under assumption 2 (comparatively high doses) if they did not have the outcome of interest. This imposed a strong negative dose-response relationship among the out-of-area participants.

These two scoping analyses were intended to represent a wide but plausible range of impact that the out-of-area participants might have on the estimated dose-outcome relationships.

C.1.b. Inferences About Dose-response Relationships: Models for Objective 2

Generalizations of the logistic regression model [2] were examined to identify and account for confounding and effect-modifying factors in the analyses of disease outcomes and thyroid UDAs. These generalizations permitted the background probabilities to depend on factors in addition to sex (e.g., year of birth, age at HTDS examination, smoking, and other thyroid radiation exposure), and the regression coefficient to depend on those factors as well as sex. To model effects on the background probabilities, A_j was replaced with an expression of the form $a'x$, where x is a vector with components representing the stratification and the additional factors to be considered and a is a vector of corresponding regression coefficients. Similarly, to model effects on the regression coefficient (i.e., to identify effect-modifying factors), the regression coefficient B was replaced by an expression of the form $b'z$, where z is a vector with components representing the factors being considered.

C.1.c. Inferences About Dose-response Relationships: Models for Objective 3

Alternatives to model [1] were considered in order to investigate the shapes of any exposure-response relationships that were found. These included the logistic model [2] and the linear-quadratic model [5] described above.

C.1.d. Inferences About Dose-response Relationships for Numbers of UDAs

Additional analyses of ultrasound-detected thyroid abnormalities (thyroid UDAs) were performed to investigate whether the average number of abnormalities above a given size might increase with increasing radiation dose to the thyroid. For these analyses, each participant's number of such UDAs was assumed to follow a Poisson distribution with mean value $M_j(d)$ for participants in stratum j with dose d, where

$$M_j(d) = \exp(A_j + B \times d).$$

C.2. Calculational Methods for Inferential Analyses

No previous epidemiological studies have dealt with exposure data of the kind available for this study, i.e., correlated sets of multiple realizations of estimated dose for the in-area participants; and no specific dose estimates for an appreciable number of participants (the out-of-area group). Two sets of analyses were performed:

- The first set of analyses used single dose estimates for each living evaluable participant. In particular the median dose estimates (d_i as defined in section VIII.B.3.a above) were used as the primary point estimate of each participant's thyroid radiation dose from Hanford's ^{131}I. This approach, which is generally analogous to that used for the main published analysis of results from the Utah Study (67), ignored the uncertainty of the dose estimates and might therefore be expected to introduce bias into estimation of dose-response relationships. However this analysis had several advantages: it corresponded to the manner in which dose-response relationships were displayed in the tabular and graphical formats; it was analogous to analyses that have been performed for other studies of the effects of radiation on thyroid disease; and it was expected to provide reasonably accurate significance test results (as observed empirically [67]).

- The second set of analyses investigated the effects of uncertainty in the estimated doses from Hanford's ^{131}I. It was expected that this would have little impact on the results of significance tests of dose-response relationships.

These two sets of analyses are described in more detail in the following section.

C.2.a. Analyses Ignoring Dose Uncertainties

For the analyses ignoring dose uncertainties, the primary method for calculating parameter estimates was the method of maximum likelihood. In addition, however, certain analyses were performed using an alternative method, the method of least squares. Maximum likelihood and least squares are two generally applicable methods for estimating parameters of statistical models, including dose-response models. The specific implementations of these methods for HTDS are described in the following sections.

C.2.a.1. Maximum Likelihood Analyses of the Sex-stratified Linear Probability Model

Maximum likelihood estimates were calculated for the sex-stratified linear probability model [1] for disease outcomes and thyroid UDAs. As described in section VIII.C.1.a, the possible values of the sex-specific background rates A_1 and A_2 and of the slope B are constrained by the requirement that probabilities $P_j(d)$ must lie between 0 and 1. For example, if the background disease rates are low and there are few or no cases at the high end of the dose range, the regression parameter B in [1] is likely to be negative (e.g., $B < 0$). If it is too negative, there will be some study participants whose estimated probabilities are less than 0. To reduce difficulties that could arise from attempting to maximize the likelihood function under this constraint, estimation was based on the profile likelihood function. Let $L(A_1, A_2, B)$ denote the log-likelihood function, i.e., the logarithm of the probability of the observed outcome data given the doses and parameter values A_1, A_2, and B:

$$[7] \qquad L(A_1, A_2, B) = \Sigma_i \{ Y_i \times \ln[P_{j(i)}(d_i)] + (1 - Y_i) \times \ln[1 - P_{j(i)}(d_i)] \}$$

where d_i denotes the estimated thyroid radiation dose of participant i, j(i) is the stratum of participant i, and Y_i is an indicator variable for the outcome of interest, i.e., $Y_i = 1$ if the disease of thyroid UDA is detected in participant i, and $Y_i = 0$ otherwise. In [7] the summation is taken over $i = 1, \ldots, N$ where N is the

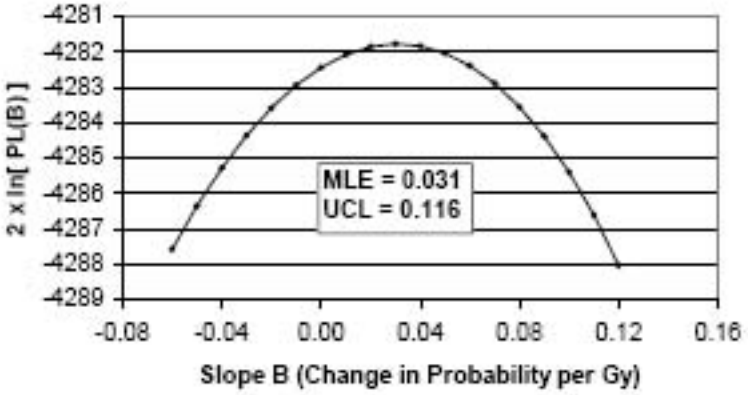
number of living evaluable in-area participants. Note that the parameters to be estimated enter [7] through the sex-stratified linear model for $P_{j(i)}(d)$, i.e., equation [1]. For a given value of the slope parameter B, the log-likelihood [7] varies as a function the two background rates A_1 and A_2. Let $A_{1,max}(B)$ and $A_{2,max}(B)$ denote the values of A_1 and A_2 for which $L(A_1, A_2, B)$ is maximized (again for the given value of B). Then the profile log-likelihood function can be written as

$$PL(B) = L[A_{1,max}(B), A_{2,max}(B), B] .$$

Note that the profile log-likelihood is simply a function of a single parameter, the slope B.

The maximum likelihood estimates of all three parameters of the sex-stratified linear probability model can be obtained by finding B_{MLE}, the value of B for which PL(B) is maximized. The maximum likelihood estimates of the background rates are then simply $A_{j,MLE} = A_{j,max}(B_{MLE})$ for j = 1 and 2. Figure VIII.C-1 below illustrates the profile log-likelihood function for the outcome of any thyroid ultrasound-detected abnormality (UDA; see section IX.P.2 below for the complete analysis of this outcome).

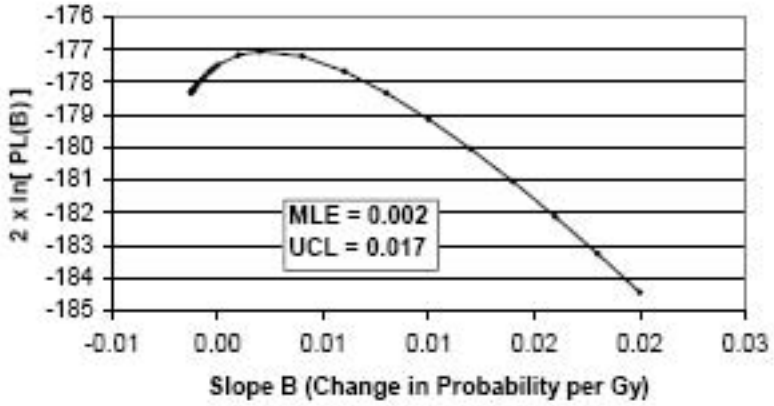
Figure VIII.C-1. Profile Log-likelihood Function for Any Thyroid UDA



The vertical axis displays the value of the natural logarithm of the profile likelihood function, PL(B), multiplied by 2, since this value is used for significance testing and confidence interval calculation as described below. MLE = maximum likelihood estimate, UCL = upper confidence limit (see section VIII.C.2.b.1 below).

Note that since conversion to logarithms and multiplication by 2 are monotone increasing transformations, the value of B which maximizes the curve in Figure VIII.C-1 also maximizes the profile likelihood function itself, and is therefore the maximum likelihood estimate of the slope. The example of any thyroid UDA in Figure VIII.C-1 above is comparatively well-behaved. That is, the maximum of the profile likelihood function is clearly evident, with values decreasing sharply and fairly symmetrically for either smaller or larger values of the slope B. This occurred because the background prevalence of any thyroid UDA was relatively high. Therefore the requirement that probabilities lie between 0 and 1 imposed no practical constraint. The situation was somewhat different for disease outcomes with low background probabilities. Figure VIII.C-2 displays the profile log-likelihood function for the outcome of thyroid cancer (see section IX.C below for the complete analysis of this outcome).

Figure VIII.C-2. Profile Log-likelihood Function for Thyroid Cancer

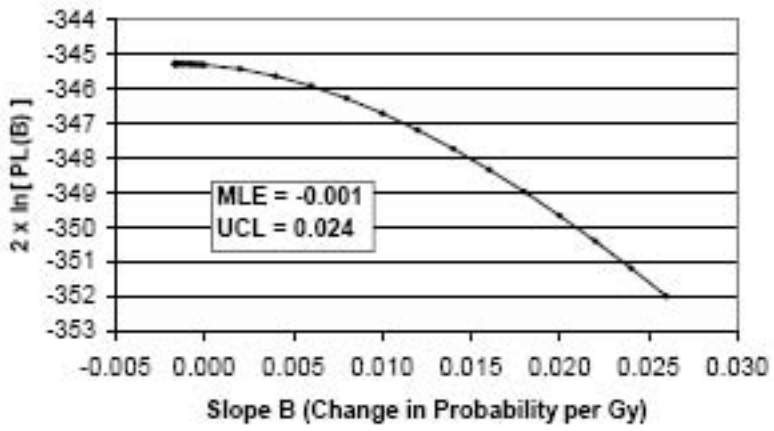


The vertical axis displays the value of the natural logarithm of the profile likelihood function, PL(B), multiplied by 2, since this value is used for significance testing and confidence interval calculation as described below. MLE = maximum likelihood estimate, UCL = upper confidence limit (see section VIII.C.2.b.1 below).

In contrast to the relatively high prevalence of thyroid UDAs, the background probabilities of thyroid cancer are low: only 14 (0.4%) of the 3191 living evaluable in-area participants had diagnoses of thyroid cancer based on the primary diagnostic definition (see section IX.C below). Therefore, due to the constraint described above, the profile likelihood function begins to decrease precipitously for increasingly negative values of the slope B. Nevertheless the value of B for which the profile likelihood is maximized is clearly evident.

Figure VIII.C-3 below displays the profile log-likelihood function for the outcome of Graves disease, which like thyroid cancer is relatively uncommon: 32 (1.0%) of the 3191 living evaluable in-area participants had diagnoses of Graves disease based on the primary diagnostic definition (see section IX.I. below). In this case the maximum likelihood estimate of B was slightly negative, and the profile likelihood function decreases very rapidly for even slightly more negative values of B.

Figure VIII.C-3. Profile Log-likelihood Function for Graves Disease



The vertical axis displays the value of the natural logarithm of the profile likelihood function, PL(B), multiplied by 2, since this value is used for significance testing and confidence interval calculation as described below. MLE = maximum likelihood estimate, UCL = upper confidence limit (see section VIII.C.2.b.1 below).

Computer programs were written by HTDS staff to fit models of the sex-stratified linear probability model [1] using the Newton-Raphson method to maximize the profile likelihood function. Likelihood ratio tests based on the profile likelihood function were used to test the statistical significance of the dose-response relationships in these analyses. Specifically, the test statistic was

$$\chi^2 = 2 \times \{ \ln[\, PL(0) \,]) - \ln[\, PL(B_{MLE}) \,] \} \,,$$

which, under the null hypothesis that the slope is 0, has a chi-square distribution with 1 degree of freedom. P-values for testing the one-sided alternative hypothesis that risk increases with increasing dose were calculated as

$$P = [\, 1 - F_1(\chi^2) \,] / 2, \text{ if } B_{MLE} \geq 0$$

$$[\, 1 + F_1(\chi^2) \,] / 2, \text{ if } B_{MLE} < 0 \,,$$

where $F_1(\bullet)$ is the cumulative distribution function of the chi-square distribution with 1 degree of freedom. Confidence intervals for the parameters of the sex-stratified linear probability model were calculated as described in VIII.C.2.b.1 below.

C.2.a.2. Maximum Likelihood Analyses of Logistic Models

The parameters of logistic dose-response models of the form [2] and its generalizations for analyses of possible confounding and effect modification (see section VIII.C.1.b above) were estimated using SAS PROC LOGISTIC, a commercially available program for fitting logistic regression models.

Logistic regression models were also used to analyze disease outcomes in relation to alternative representations of exposure, i.e., by geostratum and by the dichotomous exposure variable described in section VIII.B.3.b above. For analyses by geostratum, each living evaluable participant was assigned a vector of eight indicator variables:

$G_{i,1}$ = 1 if participant i had geostratum Pasco/Kennewick, = 0 otherwise,

$G_{i,2}$ = 1 if participant i had geostratum Walla Walla City, = 0 otherwise, etc.

Note that these eight indicator variables all had value 0 for participants in the Richland geostratum. A similar indicator variable was defined for participants in the high or low exposure groups:

H_i = 1 if participant i is in the high exposure group, = 0 otherwise.

In both of these analyses age at the time of HTDS examination was included in the regression model. This was done because the nine geostrata differed slightly in their participants' average ages at examination, as did the high and low exposure groups (see section IX.A.7). Since cumulative incidence of thyroid diseases and prevalence of thyroid UDA increase with age, age at HTDS examination was included in order to adjust for its possible confounding effect. The sex-stratified age adjusted logistic regression models that allowed the cumulative incidence of disease outcomes or prevalence of thyroid UDA outcomes to vary among the geostrata or between the high and low exposure groups were then

$$P_{j(i)}(d_i) = \exp[\, A_{j(i)} + B_c \times C_i + \Sigma_g (B_g \times G_{i,g}) \,] \,/\, \{1 + \exp[\, A_{j(i)} + B_c \times C_i + \Sigma_g (B_g \times G_{i,g}) \,] \}$$

and

$$P_{j(i)}(d_i) = \exp(\, A_{j(i)} + B_c \times C_i + B \times H_i \,) \,/\, [1 + \exp(\, A_{j(i)} + B_c \times C_i + B \times H_i \,) \,] ,$$

respectively, where

C_i = age at HTDS examination for participant i.

C.2.a.3. Maximum Likelihood Analyses of Dose-Response Models for Laboratory Values, Thyroid Mass, and Numbers of UDAs

Since laboratory values and thyroid mass are quantitative variables, some of which are subject to censoring, their dose response models [4] were analyzed using SAS PROC LIFEREG, which calculates maximum likelihood estimates of parameters for parametric models. Maximum likelihood estimates were also calculated for the Poisson regression model used to analyze numbers of thyroid UDAs as described in section VIII.C.1.d above; the statistical program SPlus® was used for these calculations.

C.2.a.4. Least Squares Analyses

The method of least squares is another general method for estimating parameters in statistical models, an alternative to the method of maximum likelihood. SAS PROC REG was used to perform unweighted least squares analyses for three types of analysis of HTDS data. The first was to estimate the parameters of the sex-stratified linear probability model [1]. This analysis, designated the least squares analysis of ungrouped data ("LSU"), used the same data as in the profile likelihood analyses described in section VIII.C.2.a.1 above, i.e., the individual dose estimates and disease outcome data for each living evaluable participant.

For the second analysis, designated the least squares analysis of grouped data ("LSG"), the living evaluable in-area participants were grouped into eight dose categories, with cutpoints at 10, 50, 100, 150, 200, 300, and 400 mGy. The arithmetic means of the estimated thyroid doses of the participants in each category were then calculated separately for women and men. These average doses were then substituted for the individual dose estimates in the sex-stratified linear probability model [1].

The third use of least squares was to estimate the parameters of the linear-quadratic dose-response model [5].

C.2.b. Confidence Intervals

Confidence intervals were calculated for all estimates of background rates and dose-response slopes or regression coefficients. The method used to calculate confidence limits depended on the model and method of estimation, as described below. In addition, since three or more parameters were estimated for each model considered, confidence intervals were adjusted for the simultaneous estimation of multiple parameters as described in section VIII.C.2.b.4 below.

C.2.b.1. Linear Probability Model

As described above in section VIII.C.2.a.1, the parameters of the sex-stratified linear probability model [1] were estimated by maximizing the profile likelihood function. The profile likelihood function was also used to calculate confidence limits as follows:

$$B_{LCL} = \max\{\, B \mid B < B_{MLE} \text{ and } \ln[\, PL(B)\,] \le \ln[\, PL(B_{MLE})\,] - 0.5 \times Q(c_B\,,\, 1)\,\} \text{ and}$$
$$B_{UCL} = \min\{\, B \mid B > B_{MLE} \text{ and } \ln[\, PL(B)\,] \le \ln[\, PL(B_{MLE})\,] - 0.5 \times Q(c_B\,,\, 1)\,\}\,,$$

where

B_{LCL} is the lower confidence limit for the slope,
B_{UCL} is the upper confidence limit for the slope,
B_{MLE} is the maximum likelihood estimate of the slope,
c_B is the confidence level (see VIII.C.2.b.4 below), and
$Q(c_B\,,\, 1)$ is the c_B-th percentile of the chi-square distribution with 1 degree of freedom

Confidence limits for the two sex-specific intercepts were calculated as

[8] $A_{j,LCL} = A_{j,MLE} - Z[(100 + c_B)/2] \times SE(A_{j,MLE})$ and
$A_{j,UCL} = A_{j,MLE} + Z[(100 + c_B)/2] \times SE(A_{j,MLE})$, for j = 1, 2,

where

$A_{j,LCL}$ is the lower confidence limit for the sex-specific intercept A_j,
$A_{j,UCL}$ is the upper confidence limit for A_j,
$A_{j,MLE}$ is the maximum likelihood estimate of A_j,
$SE(A_{j,MLE})$ is the estimated standard error of $A_{j,MLE}$,
c_B is the confidence level (see VIII.C.2.b.4 below), and
$Z[(100 + c_B)/2]$ is the $[(100 + c_B)/2]$-th percentile of the standard normal distribution.

C.2.b.2. Logistic Models

Confidence intervals for parameters of logistic dose-response model [2] and its generalizations for analyses of confounding and effect modification were calculated from the parameters estimates and their estimated standard errors. For example, for the simple logistic dose-response model [2], confidence limits for the regression coefficient were calculated as

[9] $B_{LCL} = B_{MLE} - Z[(100 + c_B)/2] \times SE(B_{MLE})$ and
$B_{UCL} = B_{MLE} + Z[(100 + c_B)/2] \times SE(B_{MLE})$,

where

B_{LCL} is the lower confidence limit for the regression parameter,
B_{UCL} is the upper confidence limit for the regression parameter,
B_{MLE} is the maximum likelihood estimate of the regression parameter,
$SE(B_{MLE})$ is the estimated standard error of B_{MLE} ,
c_B is the confidence level (see VIII.C.2.b.4 below), and
$Z[(100 + c_B)/2]$ is the $[(100 + c_B)/2]$-th percentile of the standard normal distribution.

Confidence limits for the intercept parameters A_1 and A_2 in logistic models were calculated using [8], and converted into confidence limits for the background rates (see [3] above) as follows:

$P_{i,LCL}(0) = \exp(A_{j,LCL}) / [\ 1 + \exp(A_{j,LCL})\ ]$ and
$P_{i,UCL}(0) = \exp(A_{j,UCL}) / [\ 1 + \exp(A_{j,UCL})\ ]$ for j = 1, 2.

C.2.b.3. Models Fit by Method of Least Squares

For parameters estimated by the method of least squares, confidence intervals were calculated using [9] for the coefficients of dose terms and [8] for intercept terms. For linear-quadratic models, confidence intervals for the coefficients of the linear and quadratic terms were calculated as:

[9] $B_{t,LCL} = B_{t,MLE} - Z[(100 + c_B)/2] \times SE(B_{t,MLE})$ and
$B_{t,UCL} = B_{t,MLE} + Z[(100 + c_B)/2] \times SE(B_{t,MLE})$,

where

$B_{t,LCL}$ is the lower confidence limit for the coefficient of the linear (t=1) or quadratic (t=2) term,
$B_{t,UCL}$ is the upper confidence limit for the coefficient of the linear (t=1) or quadratic (t=2) term,
$B_{t,MLE}$ is the least sqaures estimate of the regression coefficient, for t = 1 or 2,
$SE(B_{t,MLE})$ is the estimated standard error of $B_{t,MLE}$,
c_B is the confidence level (see section VIII.C.2.b.4 below), and
$Z[(100 + c_B)/2]$ is the $[(100 + c_B)/2]$-th percentile of the standard normal distribution.

C.2.b.4. Confidence Level and Bonferroni Adjustment

The goal in calculating confidence intervals was to achieve a nominal 95% confidence level. However when confidence intervals with a given nominal confidence level are calculated simultaneously for more than one parameter of a model, the probability that all of the intervals contain the true values of their respective parameters is less than the nominal confidence level. For example, if 95% confidence intervals are to be calculated for each of the three parameters of the simple sex-stratified linear probability model [1] (i.e., the slope and the two sex-specific background rates), the probability that all three intervals will contain their true parameter values is less than 95%. In order to adjust for this effect of estimating multiple parameters, the Bonferroni method was used. In this method confidence intervals are calculated at a confidence level higher than the nominal level in order to ensure that the probability that all confidence intervals for a given model contain their respective true parameter values is not less than the nominal confidence level. Specifically, if confidence intervals are calculated for k parameters, then to achieve an overall confidence level no less than c, each confidence interval is calculated using confidence level

$c_B = 1 - (\ 1 - c\ ) / k$.

Thus for models with three parameters, in order to ensure overall confidence level no less than c = 95%, the three confidence intervals are each calculated at level $c_B = 98.33\%$. For models with four or five parameters, $c_B = 98.75\%$ or 99%, respectively.

Since $c_B > c$, each parameter's Bonferroni-adjusted confidence interval is wider than its unadjusted interval. In particular, upper confidence limits for slopes and dose-response regression parameters are higher with the Bonferroni adjustment than without.

C.2.c. Analyses of the Effect of Dose Uncertainties

It has long been recognized that the estimation of parameters in regression models such as the linear probability model [1] or the logistic model [2] is subject to bias if an independent variable (thyroid dose in this case) is observed with nonsystematic error, i.e., with an uncertainty that does not tend to systematically reduce or increase the values of the independent variable. In general, the effect of such error is to "attenuate" the estimate of the regression coefficient. That is, if the outcome variable tends to increase as the true value of the independent variable increases, the regression coefficient will tend to be underestimated. This phenomenon was observed by Kerber et al. (67) in their analysis of the Utah Thyroid Study. Significance tests can also be affected by error in the independent variable, although this is usually less of a problem.

A number of approaches have been devised over the years to deal with this problem, i.e., to correct or "deattentuate" estimates of regression coefficients. An approach analogous to that taken in the Utah Thyroid Study (133, 134) was used to calculate "deattentuated" estimates of the regression coefficient B.

C.2.c.1. *General Approach*

The general approach of the Utah Thyroid Study (67) was followed in reporting the results of dose-response analyses. That is, the main results were based on analyses that used point estimates of dose and ignored dose uncertainty. The additional analyses that adjusted for dose uncertainties were performed to illustrate how that adjustment affects the estimates and statistical significance of the dose-response relationships. Reporting results based on analyses that ignored uncertainties in the estimated thyroid doses from Hanford's ^{131}I was important for two reasons.

- The results of the conventional analyses (e.g., fitted dose-response functions based on the participants' median or mean doses) will be useful if one attempts to generalize from HTDS cohort to other persons with thyroid doses estimated by the CIDER program. The median dose estimate can then be applied to the corresponding HTDS estimates of dose-response functions from the conventional analysis. They cannot, however, be applied to the estimates based on the extended analysis that adjusts for uncertainty.

- The results of the conventional analysis will be comparable to the main results of the Utah Thyroid Study, which were reported in terms of mean doses (67).

C.2.c.2. Descriptive Analysis of Effects of Dose Uncertainty

To illustrate how the uncertainty of estimated doses influenced the fitted dose-response relationships, the linear dose-response models [1] were fit using each of the 100 realizations of dose separately. The point estimates of and Bonferroni-adjusted 95% confidence intervals for B, the slope parameter representing the magnitude of the radiation effect, were displayed graphically to illustrate how the estimate varied among the 100 realizations of dose, and how the estimates from the 100 realizations compare to those based on the average doses.

C.2.c.3. Estimation of B with Adjustment for Dose Uncertainty

A Bayesian approach was used to calculate "deattentuated" estimates of the regression coefficient B in the sex-stratified logistic model [2]. This approach specifies the relationship among observed data (outcomes and estimated thyroid doses), unobserved data (the participants' true doses), and the parameters of distributions governing the observed and unobserved data. Specifically, let GM_i and GSD_i denote the geometric mean and geometric standard deviation of the i-th participant's 100 dose estimates, as defined in section VIII.B.3. above, and let T_i denote the logarithm of the unobserved true dose ("true log dose") of participant i. The analysis was performed under the following assumptions.

(i) The logarithm of each participant's geometric mean dose, i.e., the arithmetic mean of the logarithms of his or her 100 dose estimates, is normally distributed with mean T_i and variance $\ln^2(GSD_i)$:

$$\ln(GM_i) \sim N(T_i , \ln^2(GSD_i)) \text{ for } i = 1, \ldots, N.$$

(ii) The true log doses T_i are themselves normally distributed with means and variances that differ between G subgroups of participants:

$$T_i \sim N(M_{g(i)} , V_{g(i)}) \text{ for } i = 1, \ldots, N,$$

where $g(i) \subset \{1, \ldots, G\}$ is the index of the subgroup containing participant i. The parameters of the underlying distributions of true log doses, i.e., M_g and V_g for $g = 1, \ldots, G$, are of course unknown and must be estimated.

(iii) Given the participant's true dose, the probability of the disease outcome or thyroid UDA outcome of interest is independent of his or her estimated dose, i.e., for each living evaluable in-area participant $i= 1, \ldots, N$, the probability of the outcome is given by

$$\text{Prob}(Y_i \mid GM_i , T_i) = \exp(A_{j(i)} + B \times T_i) / [1 + \exp(A_{j(i)} + B \times T_i)] ,$$

where Y_i is the indicator of the outcome ($Y_i = 1$ if the participant has the outcome, otherwise $Y_i = 0$).

(iv) To complete the specifications necessary to implement the Bayesian approach, relatively uninformative prior distributions were assigned for the regression parameters (A_1, A_2, and B) and the means of the distributions of true log doses ($M_1, \ldots, M_G$), i.e., normal distributions with mean 0 and variance 10^6. Since the variance V of the distributions of true log doses is required to be greater than 0, its prior distribution was taken to be the gamma distribution with shape parameter 0.001 and scale parameter 10^6.

For assumption (ii), the subgroups of participants were defined so that they would be likely to have different underlying distributions of true log doses. In particular the subgroups were defined by geostrata and year of birth strata as follows:

Subgroup 1 (relatively high doses): Richland, Pasco/Kennewick, and Benton, Franklin, and Adams County geostrata, and 1940-1945 birth year strata.

Subgroup 2 (intermediate doses): Richland, Pasco/Kennewick, and Benton, Franklin, and Adams County geostrata, and 1946 birth year strata; or Walla Walla City or County geostrata, and 1940-1945 birth year strata.

Subgroup 3 (relatively low doses): Walla Walla City or County geostrata, and 1946 birth year strata; or Okanogan and Ferry/Stevens County geostrata (any birth year strata).

In addition, the distributions of true doses in (ii) were assumed to have common variance V, i.e., $V_g = V$ for g = 1, …, G.

The objective of the Bayesian approach was to estimate the posterior marginal distribution of the regression parameters, conditional on the observed data, i.e., on the values of Y_i, GM_i, GSD_i for i = 1, …, N. This was accomplished using the Gibbs sampling technique, as implemented by the freeware WinBUGS package (available at http://www.mrc-bsu.cam.ac.uk/bugs).

To begin the Gibbs sampling, initial values were specified as follows:

$B = 0$,
$A_j = \ln[\, b_j / (1 - b_j)\,]$ for j = 1 or 2, where b_j is the proportion of participants of sex j with the outcome, and
$T_i = \ln(GM_i)$ for i = 1, …, N .

The initial values of the means of the distributions of log true doses for the three subgroups were simply the means of $\ln(GM_i)$, which are summarized in the following table:

Table VIII.C-2 Description of Log True Doses for Subgroups 1– 3

Subgroup	No. of Living Evaluable In-Area Participants	Mean of $\ln(GM_i)$	Variance of $\ln(GM_i)$
1	2173	-2.27	3.33
2	646	-2.82	1.28
3	372	-4.41	2.51

Based on the variances of $\ln(GM_i)$ in the three subgroups, the initial value of the common variance V was defined as 2.5.

With these initial values, the Gibbs sampler was run for 2000 "burn-in" iterations, then for 5000 iterations to provide the estimated posterior marginal distribution of the regression parameters conditional on the observed data. In particular, the median of the 5000 values of B from its estimated marginal distribution was used to provide a "de-attenuated" estimate of the dose-response coefficient. In addition, the percentiles of that marginal distribution were used to provide an empirical confidence interval for the regression coefficient. Specifically, in order to obtain empirical confidence limits adjusted by the Bonferroni technique for the simultaneous estimation of three parameters (see section VIII.C.2.b.4 above), the percentiles at the 0.83% and 99.17% levels, i.e., the 41st and 4959th largest values of B, were defined as the confidence limits. Finally, a one-tailed empirical p-value was calculated as the proportion of the 5000 realizations for which the simulated value of B was less than 0.

C.2.c.4. Out-of-Area Participants

The approach described above applies only to analyses limited to the in-area participants, i.e., to those for whom the CIDER program provides 100 realizations of estimated dose. No attempt was made to calculate deattenuated estimates of the dose-response relationships using both the in-area and out-of-area participants.

D. Exposures from the Nevada Test Site

The ability to estimate thyroid doses caused by fallout ^{131}I from the Nevada Test Site (NTS) became available during the course of HTDS, as described in section VIII.B.2.h above. This section describes the way that information about exposures to fallout ^{131}I from the NTS was used in the HTDS.

D.1. General Approach

The general approach was to treat exposure to ^{131}I from the NTS as a potential confounding factor or effect modifier. Therefore the primary analyses of exposure-outcome relationships remained as described above. Moreover the analysis of potential confounding and effect modification by NTS exposures was performed basically as described for other potential confounders. However some special steps were necessary for analyses involving the NTS exposures; these steps are described below.

The decision to treat NTS exposure as a potential confounding or effect-modifying factor meant that certain other analyses that might be considered possible were not performed.

- No attempt was made to estimate, or test the statistical significance of, dose-response relationships between thyroid disease outcomes (or other response variables) and estimated NTS doses. This was because the HTDS cohort was defined to provide adequate statistical power for investigating the effects of Hanford doses, not NTS doses. Therefore it was very likely to be inadequate for the latter purpose.

- No analyses were conducted in which estimates of Hanford and NTS doses were added together or otherwise combined for use as the exposure variable. There were two reasons for this: 1) the objectives of HTDS refer specifically to the effects of doses from Hanford, and 2) it is not clear that dose estimates from the two dosimetry systems are comparable, and is it not known how to combine the estimates of uncertainty of the two doses.

D.2. Handling of Disease Outcome Variables in Analyses Involving NTS Doses

Exposures to ^{131}I from Hanford and the NTS occurred over a prolonged period of time. Therefore careful consideration was given to the handling of outcomes that were determined while exposure was still occurring.

No special handling was necessary to accommodate NTS exposures in the analyses of the prevalence of thyroid UDAs, since these were based on the HTDS examination, long after the cessation of Hanford and NTS exposures. However, for disease outcomes the situation was different, since diagnoses might have occurred before the end of 1957, i.e., before the end of the period for which estimated doses from NTS fallout were calculated (see section VIII.B.2.h above). As described in section VIII.C.1.a above, the primary analysis of each disease outcome was based on the cumulative incidence of the outcome among living evaluable participants. "Cumulative incidence" referred specifically to the percentage of living evaluable participants with the outcome of interest diagnosed at any time up to and including the HTDS examination.

One possible alternative to the use of cumulative incidence was to perform an "incidence study," i.e., to analyze incidence rates (cases per 100,000 person-years). The use of incidence rates is a standard epidemiological method that has been successfully applied in a number of studies of radiation effects. It is often particularly appropriate when exposure occurs over a prolonged period. However when the HTDS protocol and Analysis Plan were developed (i.e., prior to the availability of information about exposures to ^{131}I from the NTS), two major reasons were identified that argued against trying to perform an incidence study.

- Dates of many past diagnoses (i.e., diagnoses made prior to the participant's HTDS examination) were likely to be imprecisely known. This was expected to be true to varying degrees for diagnoses documented in medical records. Reports of past diagnoses based solely on the In-Person Interview of the participant or the CATI were likely to be especially imprecise.

- The age profiles of incidence rates were likely to be distorted by the occurrence of HTDS examinations. NCRP has noted that tumor registries may underestimate the true incidence of thyroid cancer by a factor of three (45). Thus it was expected that the highly sensitive HTDS examinations would induce an apparent sharp jump in age-specific incidence rates of neoplastic diseases. This was anticipated for non-neoplastic diseases as well.

  In addition, a third enabling reason was identified. While this reason did not argue against analyzing incidence rates, it did provide a rationale for the use of cumulative incidence.

- The bulk of the Hanford exposure occurred before 1950, while the vast majority of diagnoses likely occurred later. Therefore an analysis of cumulative incidence, which in effect treats all diagnoses as occurring after completion of exposure, was unlikely to be seriously biased.

When the decision was made to include the NTS exposure as a potential confounding or effect modifying factor, the applicability of these reasons was re-examined. The first two reasons remained strong arguments against conducting an incidence study. However the third reason was more problematic: since the NTS exposures occurred primarily between 1952 and 1957, the likelihood that some diagnoses occurred before the end of exposure was increased (HTDS participants were 11 to 18 years old at the end of 1957). Therefore the decision was made to modify analyses that include NTS exposure by considering cumulative incidence since January 1, 1958. This was accomplished for each disease outcome by excluding any participant with a diagnosis of that outcome before January 1, 1958. Implications of this decision included the following:

- Restricting the period of observation to begin on January 1, 1958, rather than at birth, might have an impact on the estimates and/or statistical significance of the dose-response relationships of interest, i.e., the associations between cumulative incidence of disease outcomes and Hanford dose. It was considered likely that any such impact would be small, since it is expected that few diagnoses occurred before 1958. For any disease outcome with no diagnoses before 1958, the modification would have no effect. For disease outcomes that included diagnoses before 1958, the effect of restricting the period of observation was examined. The age-stratified linear probability model (equation [1] above) was fit using both the unrestricted and the restricted periods of observation. In addition the generalized linear probability model including the pooled categorical variable for NTS exposure was also fit using both the unrestricted and the restricted periods of observation. The results of these four fits were compared to assess whether the choice of observation period affects the estimated effect of Hanford doses.

- To perform the modified analysis, each diagnosis had to be classified according to its date: before 1958 or after 1957. As noted in Reason 1 above, dates of many past diagnoses were known only imprecisely. However many cases with imprecisely known diagnosis dates could be accurately assigned between these two time intervals. Only a few cases could not be accurately assigned with a high degree of certainty. Each such case was assigned a diagnosis date in the middle of the range of plausible dates based on the available information, and then into one of the two time intervals on the basis of that assigned date.

IX. RESULTS

A. Characteristics of the Living Evaluable Participants

Of the 3447 eligible participants who attended an HTDS clinic, seven (0.2%) were determined to be nonevaluable according to the criteria in section IV.B above. Six did not have complete residence histories for the period from the beginning of their possible exposure to ^{131}I from Hanford through the end of 1957, and the seventh had a tracheotomy tube in place which prevented palpation of her thyroid at her HTDS clinical examination. The remaining 3440, designated the living evaluable participants, are the basis for most of the analyses reported here. For each of these 3440 participants, sufficient data were available to permit an evaluation of thyroid health and estimation of the radiation dose from Hanford's ^{131}I. Several characteristics of the living evaluable participants are summarized in Table IX.A-1. About half (50.8%) of the living evaluable participants were women. About one-fourth (26.3%) were born in 1944, and another third (34.0%) were born in 1943 or 1945. Therefore a large proportion of the living evaluable participants were infants or very young children during 1945, the years of the largest releases of ^{131}I from Hanford. At the time of their HTDS examinations, the living evaluable participants ranged in age from 45 to 57 (median 51). A large majority (97.5%) described themselves as white or Caucasian.

Table IX.A-1. Characteristics of Living Evaluable Participants

Characteristic		No.	%
Sex	Female	1747	50.8
	Male	1693	49.2
	Total	3440	100.0
Year of birth	1940	243	7.1
	1941	283	8.2
	1942	472	13.7
	1943	560	16.3
	1944	906	26.3
	1945	611	17.8
	1946	365	10.6
	Total	3440	100.0
Age at examination	45	1	--
	46	58	1.7
	47	194	5.6
	48	264	7.7
	49	323	9.4
	50	388	11.3
	51	741	21.5
	52	561	16.3
	53	278	8.1
	54	229	6.7
	55	273	7.9
	56	118	3.4
	57	12	0.3
	Total	3440	100.0
Race/ethnic origin	White/Caucasian	3354	97.5
	Black/Negro	1	--
	Asian or Pacific Islander	10	0.3
	Native American	40	1.2
	Spanish or Hispanic	5	0.1
	Other	23	0.7
	Don't Know	2	0.1
	Not Recorded	1	--
	Refused	4	0.1
	Total	3440	100.0
Religious preference	Protestant	2176	63.3
	Catholic	483	14.0
	Jewish	4	0.1
	Mormon	128	3.7
	Seventh Day Adventist	108	3.1
	Other	94	2.7
	None	437	12.7
	Not Recorded	1	--
	Refused	6	0.2
	Don't Know	3	0.1
	Total	3440	100.0

One important purpose for collecting information about the characteristics described above (as well as the other factors described below) was to use that information to test for possible confounding and effect modification in the analyses of the radiation dose-responses (see section VIII.A.1.b above). As noted above, the living evaluable participants overwhelmingly identified themselves as white or Caucasian (97.5%). Therefore, meaningful analyses of race or ethnic origin as a potential confounder or effect modifier could not be performed. In addition, Jewish religious preference was of particular interest as a potential confounder or effect modifier, since there is some evidence suggesting increased risk of thyroid cancer in Jewish populations (46). However only four (0.1%) of the living evaluable participants stated Jewish as their religious preference, so further analysis of this factor was not possible.

A.1. History of Diagnostic X-Rays, Fluoroscopy, Thyroid Nuclear Scans, and other Nuclear Medicine Procedures

Of the 3440 living evaluable participants, 3317 (96.4%) had a report, either from the In-Person Interview or the CATI, of one or more diagnostic x-rays or fluoroscopies of the upper body, thyroid nuclear scans, or other nuclear medicine procedures. The proportions with reports of specific procedures are summarized in Table IX.A-2.

Table IX.A-2. History of Diagnostic X-Rays, Fluoroscopy, Thyroid Nuclear Scans, and other Nuclear Medicine Procedures

	In-Person Interview Only		In-Person Interview and CATI	
Have You Ever Had:	No.	%♦	No.	%♦
CAT scan of the upper body?	832	24.2	*	
Diagnostic x-rays of the head?	1183	34.4	1294	37.6
Diagnostic x-rays of the neck?	1026	29.8	1045	30.4
Diagnostic x-rays of the chest or upper body, including mammograms?	3027	88.0	3045	88.5
Diagnostic x-rays of the stomach or mid-back?	745	21.7	*	
Barium enema?	887	25.8	*	
Upper GI?	1228	35.7	1236	35.9
Intravenous pyelogram or IVP?	420	12.2	425	12.4
Fluoroscopy of the upper body?	234	6.8	271	7.9
Other nuclear scan?	229	6.7	231	6.7
Any of the above?	3305	96.1	3317	96.4

* Question not asked in CATI

♦ Percent calculated in relation to number of living evaluable participants

By far the most common types of procedures were diagnostic x-rays of the chest or upper body, including mammograms, which were reported for 3045 (88.5%) of the living evaluable participants. Also particularly common were diagnostic x-rays of the head or neck, which were reported for 37.6% and 30.4%, respectively, and upper GI examinations (35.9%). Nearly one-fourth (24.2%) of the living evaluable participants reported a history of upper body CAT scan (since the CATI covered the time period ending in 1957, it did not include a question regarding CAT scans). Upper body fluoroscopies were reported for 271 (7.9%) living evaluable participants. Histories of nuclear scans other than thyroid scans were reported for 231 (6.7%) of the living evaluable participants. In addition, histories of thyroid nuclear scans, which are used to assist in the diagnosis of thyroid disorders, were reported for 142 (4.1%) of the living evaluable participants.

A.2. History of Radiation Treatment

Histories of x-ray treatment affecting the upper body for reasons other than cancer were reported for 90 (2.6%) of the living evaluable participants (Table IX.A-3). The most common reason stated was treatment of acne, reported for 37 (1.1%).

Cancer other than thyroid cancer was reported on the In-Person Interview by 276 (8.0%) of the living evaluable participants, with 42 of these 276 reporting having received radiation therapy for the cancer.

Table IX.A-3. History of Radiation Treatment

	In-Person Interview Only		In-Person Interview and CATI	
Have You Ever Had:	No.	%♦	No.	%♦
X-ray treatment to the upper body for acne?	32	0.9	37	1.1
X-ray treatment to the upper body for ringworm?	1	0.03	10	0.3
X-ray treatment for enlarged tonsils?	2	0.06	4	0.1
X-ray treatment to the upper body for tuberculosis?	2	0.06	2	0.06
X-ray treatment for scalp infection?	1	0.03	1	0.03
X-ray treatment for enlarged thymus?	0	--	7	0.2
X-ray treatment to the upper body for any other reason?	15	0.4	31	0.9
Any of the above x-ray treatments?	52	1.5	90	2.6
History of any cancer other than thyroid?	276	8.0	*	
Radiation treatment for any cancer other than thyroid?	42	1.2		

* Question not asked in CATI

♦ Percent calculated in relation to number of living evaluable participants

A.3. History of Dental X-rays

A history of dental x-ray exposure was reported for nearly all (99.2%) of the living evaluable participants, although only 346 (10.1%) reported receiving dental x-rays more frequently than once per year during their life (see Table IX.A-4). About half (51.8%) of the living evaluable participants reported on the In-Person Interview or CATI at least one time period when lead shielding of the neck was not used in dental x-ray examinations.

Table IX.A-4. History of Dental X-rays

	In-Person Interview Only		In-Person Interview and CATI	
Have You Ever Had:	No.	%♦	No.	%♦
Dental x-ray?	3406	99.0	3414	99.2
Dental x-ray more frequently than once a year?	324	9.4	346	10.1
Dental x-rays that did not usually include a lead shield over the neck area?	1727	50.2	1781	51.8

♦ Percent calculated in relation to number of living evaluable participants

A.4. Occupational History

Data regarding the participants' occupational histories were obtained from the In-Person Interview. The intention was to identify persons who had worked in occupations that might involve exposure to radiation. Therefore, results are presented for occupations in the metals industry, employment at nuclear facilities, and other occupations that might involve exposure to radioactive materials. The results are summarized in Table IX.A-5.

Table IX.A-5. Occupational History

Have You Ever Worked in Any of the Following Industries or Occupations?	Female		Male		Total	
	No.	%♦	No.	%♦	No.	%♦
Any Metal Industry	30	1.7	239	14.1	269	7.8
Geology	5	0.3	19	1.1	24	0.7
Metallurgy	7	0.4	45	2.7	52	1.5
Metal processing	15	0.9	131	7.7	146	4.2
Ore refining	2	0.1	29	1.7	31	0.9
Mining	1	0.1	60	3.5	61	1.8
Any Nuclear Facility	110	6.3	273	16.1	383	11.1
Nuclear Industry, as a civilian	84	4.8	168	9.9	252	7.3
On the premises of a nuclear facility	85	4.9	224	13.2	309	9.0
Any Area Exposed to Radioactive Materials/X-Rays	203	11.6	274	16.2	477	13.9
Health care	178	10.2	81	4.8	259	7.5
Scientist, researcher, or student	34	1.9	56	3.3	90	2.6
Military	2	0.1	123	7.3	125	3.6
Any other industry or occupation	16	0.9	66	3.9	82	2.4
Any of the Above Industries	321	18.4	636	37.6	957	27.8

♦ Percent calculated in relation to number of living evaluable participants

Of the 3440 living evaluable participants, 957 (27.8%) reported a history of employment in one or more of the occupations or facilities of interest. The proportion was higher among the men (37.6%) compared to the women (18.4%). The higher proportion among the men was largely due to occupations in the metals industry (14.1%) or employment at nuclear facilities (16.1%). The proportions of women reporting such histories were much smaller (1.7% and 6.3% respectively). The proportions of men and women reporting histories of working in areas with possible exposure to radioactive materials were more similar: 16.2% for men, 11.6% for women. Most of the women with such histories identified an occupation in the health care industry (10.2%).

A.5. Smoking History

The In-Person Interview included a series of questions regarding smoking. Of the 3440 living evaluable participants, 2053 (59.7%) reported a history of ever smoking cigarettes, cigars, and/or pipes. See Table IX.A-6.

Table IX.A-6. Smoking: History of Ever Smoking

Have You Ever Smoked	Female		Male		Total	
Any of the Following:	No.	%♦	No.	%♦	No.	%♦
Non-filter cigarettes?	180	10.3	755	44.6	935	27.2
Filter cigarettes?	880	50.4	1013	59.8	1893	55.0
Any cigarettes?	897	51.3	1103	65.2	2000	58.1
Cigars?	4	0.2	121	7.1	125	3.6
Pipe?	2	0.1	221	13.0	223	6.5
Any of the above?	897	51.3	1156	68.3	2053	59.7

♦ Percent calculated in relation to number of living evaluable participants

The proportion that reported ever smoking was higher among men (68.3%) than women (51.3%). As expected, cigarette smoking was by far the most common form, reported by all of the women who reported any kind of smoking, and by 65.2% of the 1693 living evaluable male participants. The amount of cigarette smoking was quantified in terms of pack-years. One pack-year is equivalent to smoking one pack a day for one year. When adequate data were available from the In-Person Interview, the total consumption in pack-years was calculated by integrating the reported consumption in packs per day over the years of smoking. Similar calculations were performed to quantify cigar and pipe smoking based on cigars per day and pipes (bowls) smoked per day. The results are shown in Table IX.A-7.

Table IX.A-7. Smoking: Level of Use

		Female	Male	Total
Non-filter cigarettes	Median	1.5	4	3
(pack-years)	Range	0.01-70	.0003-98.9	.0003-98.9
	Number	180	745	925
Filter cigarettes	Median	18.54	19	18.75
(pack-years)	Range	0.01-140	0.01-130	0.01-140
	Number	874	1009	1883
Any cigarettes	Median	19.5	24.1	21.25
(pack-years)	Range	0.01-140	0.01-136	0.01-140
	Number	891	1090	1981
Cigars	Median	1	6	6
(cigar-years)	Range	0.8-2	0.01-443	0.01-443
	Number	4	119	123
Pipe	Median	1.1	5.7	5.7
(pipe-years)	Range	0.7-1.4	0.1-500	0.1-500
	Number	2	217	219

Among 1981 living evaluable participants who ever smoked cigarettes and for whom adequate consumption data were available, the median total pack-years was 21.25 (range 0.01 to 140). The consumption was higher among men who smoked cigarettes, with a median of 24.1 pack-years, compared to 19.5 pack-years for women. Cigar- and pipe-smoking men reported median consumption levels of 6 cigar-years and 5.7 pipe-years. Very few women reported ever smoking cigars or pipes.

A.6. Dietary Factors

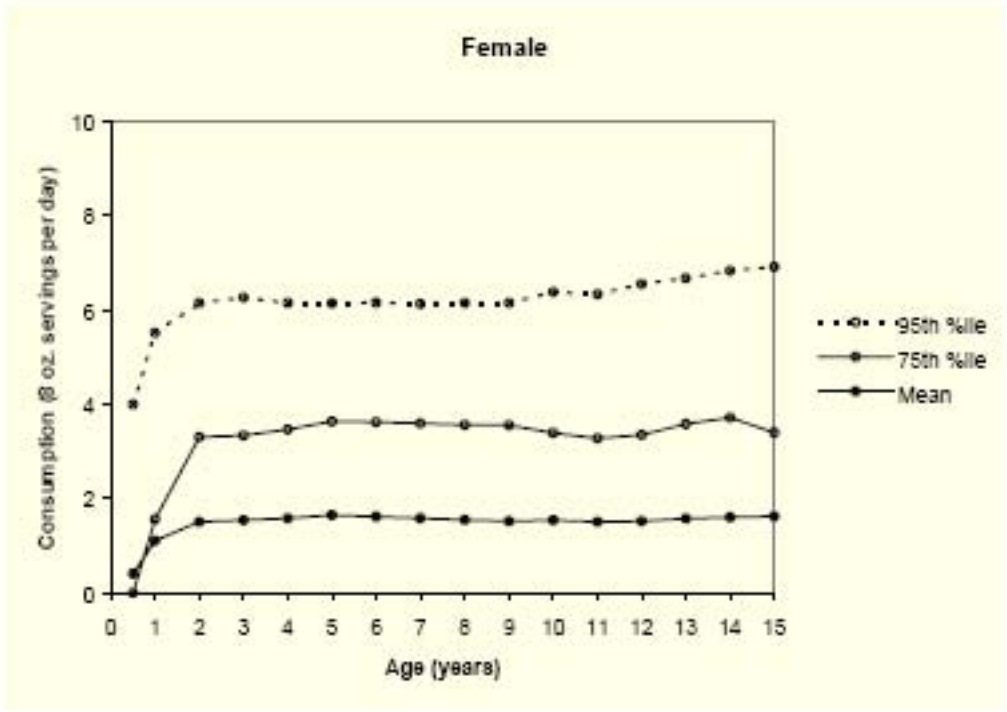
Each participant's thyroid radiation dose depends on several factors. Of particular importance is the dietary history, including the amounts of milk, milk products and other foods that the participant consumed, and the sources of those foods. Therefore, information about these dietary factors was collected as part of the CATI for use by the CIDER program in calculating estimated radiation doses. The following sections present information about the quantities of various milk and food products consumed by the 1979 living evaluable in-area participants whose CATI data were used for dose estimation, as reported by their CATI respondents. Results are shown separately for women and men. Since a participant's consumption of milk and food products typically changed over time, results are also shown by age. Specifically, descriptive statistics (mean, median, and 5^{th}, 25^{th}, 75^{th} and 95^{th} percentiles) were calculated for the reported amounts consumed on the participant's 6-month birthday and annual birthdays (first, second, etc.) through age 15. (Since CATI respondents often reported that dietary factors changed on birthdays, the values used for these analyses were in fact those reported for 5 days after the participant's birthday.) If a participant was out of area on one of these occasions, or his or her consumption was reported as unknown, then he or she was excluded from the distribution for that birthday. Similarly, if a participant's birthday occurred before December 1944 or after 1957, then he or she was excluded from the distribution for that birthday. If a participant was reported not to have consumed a given milk or food product on a given birthday, then the consumption was taken to be zero.

A.6.a. Raw Cow's Milk and Milk Products

Consumption of raw cow's milk or milk products was reported for 999 (50.5%) of the 1979 living evaluable in-area participants whose CATI data were used for dose estimation (498 women, 501 men). For 61 of these 999 participants (31 women, 30 men), the CATI respondent was unable to provide estimates of the quantity consumed. Figure IX.A-1 summarizes the distributions of raw cow's milk and milk products consumption by sex and age. Each participant's consumption, expressed as 8 oz. servings per day, was calculated from that reported for glasses of milk, other servings of milk, and milk products. At every age shown in the figures, fewer than half of the participants were reported to consume raw cow's milk or milk products, and the 5^{th} and 25^{th} percentiles and medians were consequently all zero; therefore these three statistics are omitted from the figure for clarity.

As shown in Figure IX.A-1, consumption of raw cow's milk and milk products increased sharply for both sexes until age 2, then leveled off at averages of about 1.6 and 1.9 eight oz.servings per day for women and men, respectively. For both sexes, only about 12% were reported to consume raw cow's milk or milk products at 6 months of age, and only about 28% at one year of age. At older ages the proportions of nonconsumers ranged between 33% and 40%.

Figure IX.A-1. Raw Cow's Milk Consumption, by Sex and Age

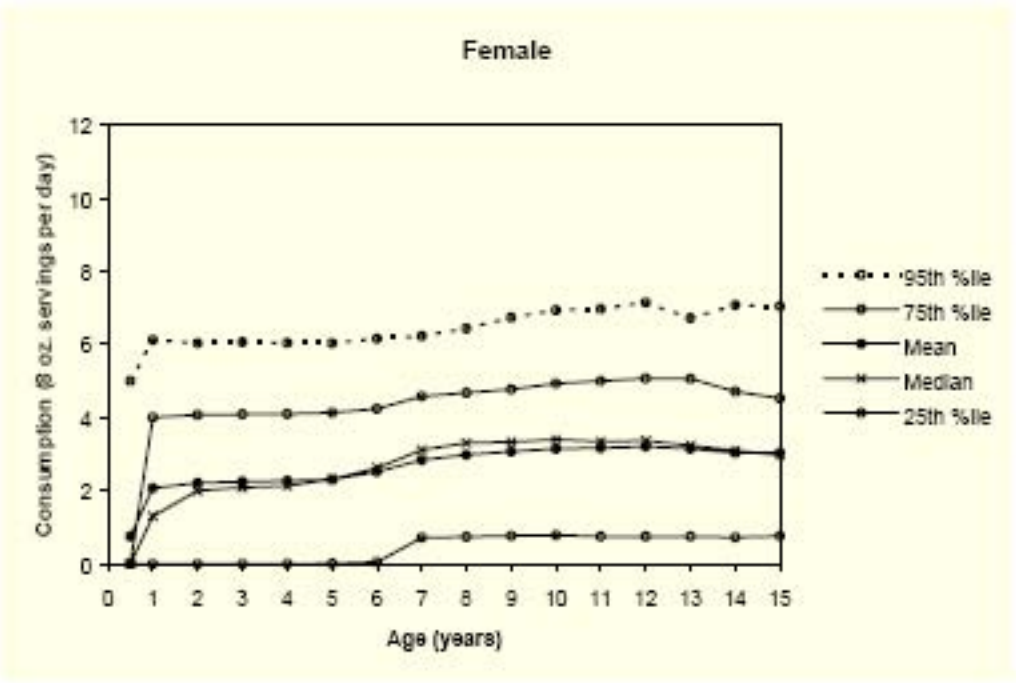


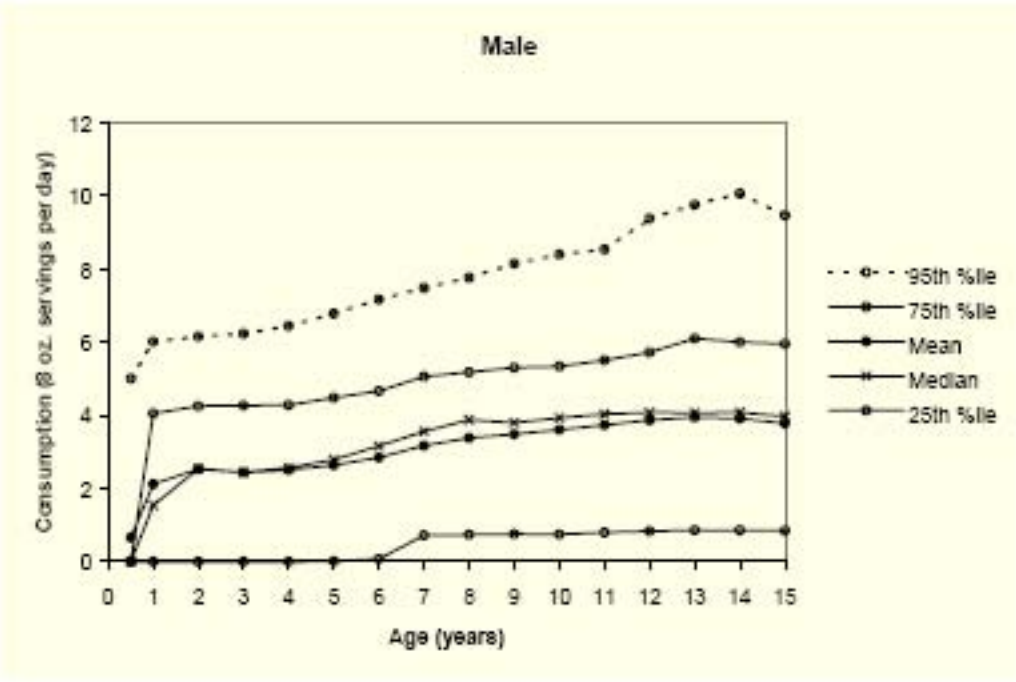
A.6.b. Processed Cow's Milk and Milk Products

Consumption of processed cow's milk or milk products was reported for 1741 (88.0%) of the 1979 living evaluable in-area participants whose CATI data were used for dose estimation (871 women, 870 men). For 86 of these 1741 (44 women, 42 men), the CATI respondent was unable to provide estimates of the quantities consumed. Figure IX.A-2 summarizes the distributions of processed cow's milk and milk products consumption by sex and age. Each participant's consumption, expressed as 8 oz. servings per day, was calculated from that reported for glasses of milk, other servings of milk, and milk products. At every age shown in the figures, more than 10% of the participants were reported to be nonconsumers of processed cow's milk or milk products, and the 5th percentiles were consequently all zero; therefore the 5th percentiles are omitted from the figure for clarity.

As shown in Figure IX.A-2, consumption of processed cow's milk and milk products increased to about 2 eight oz. servings per day at one year of age. For women, consumption remained fairly stable at this level until about age 5 or 6, then increased to about three 8 oz. servings per day. For men, consumption increased fairly steadily until the teenage years, to just under four 8 oz. servings per day. For both sexes, the proportion of nonconsumers decreased from nearly 40% at age 1 to 20% at age 6; thereafter the proportions remained fairly stable at 10 – 14%.

Figure IX.A-2. Processed Cow's Milk Consumption, by Sex and Age





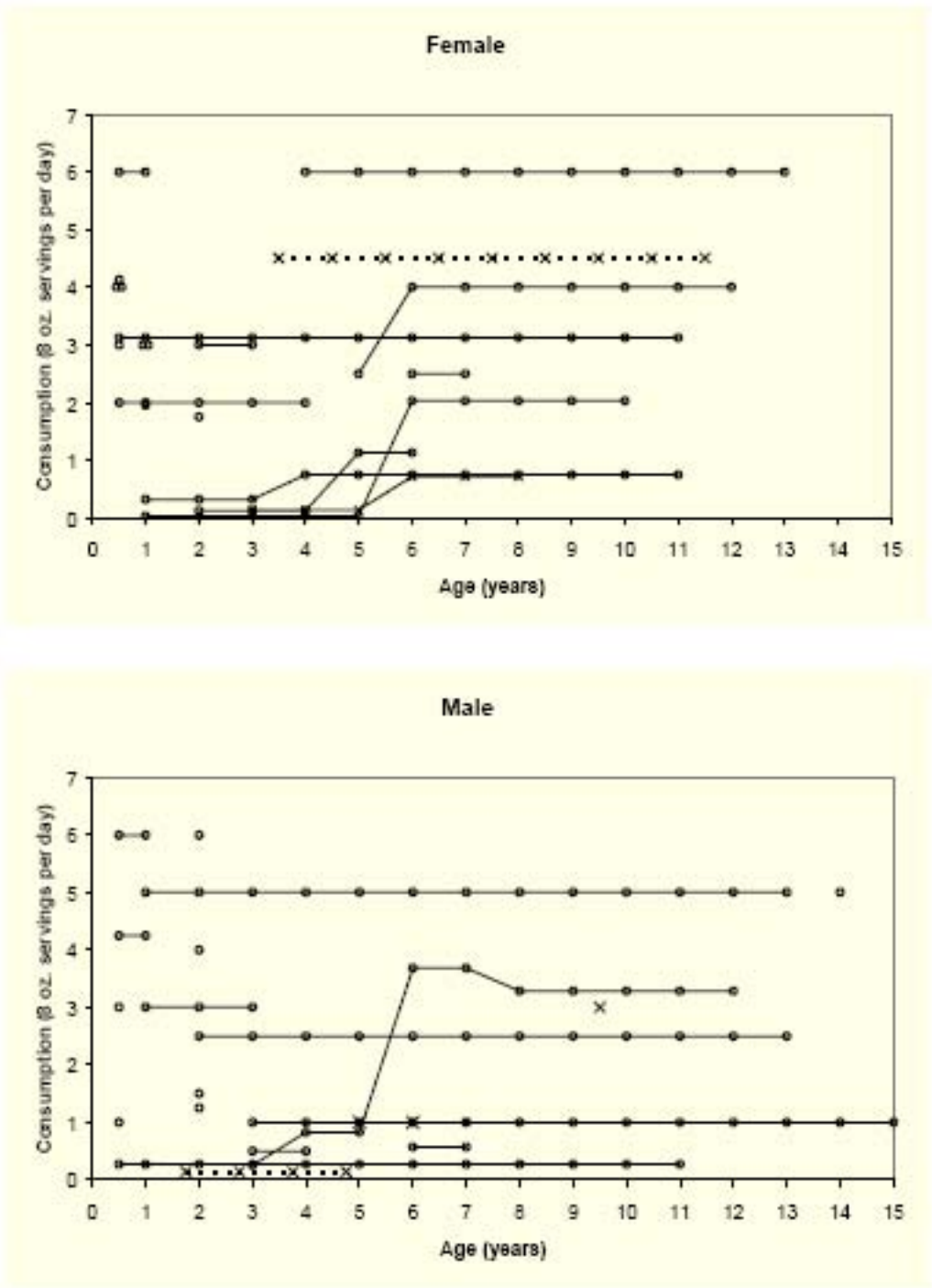
A.6.c. Goat's Milk and Milk Products

Consumption of goat's milk or milk products was reported for only 46 (2.3%) of the 1979 living evaluable in area participants whose CATI data were used for dose estimation (23 women, 23 men). For five of these 46 (three women, two men), the CATI respondent was unable to provide estimates of the quantities consumed. The reported consumption levels for the remaining 41 participants, i.e., the 20 women and 21 men for whom quantities consumed were reported, are displayed in Figure IX.A-3. Note that this figure differs from figures IX.A-1 and IX.A-2 above, since it displays the levels reported for individual participants rather than percentiles of the consumption levels.

In figure IX.A-3 below, the consumption levels reported for an individual participant at various ages are connected by lines. This was done to illustrate changes of consumption levels over time, and does not imply that every participant in the figure consumed goat's milk or milk products continuously throughout the ages indicated. For ages at which a participant was reported to be a nonconsumer of goat's milk or milk products, points are omitted from the figure for clarity. There were three participants for whom consumption of goat's milk or milk products was reported only for one or more periods of time that did not include their six-month birthday or any of their first through 15th birthdays. In order to include the participants in the figure, their consumption levels were plotted for ages at which consumption occurred. The reported consumption levels for these three participants are indicated in the figure by dashed lines and and "x" symbols. For example, one female participant was reported to have consumed about 4.5 servings of goat's milk or milk products per day between the ages of about 3.5 and 11.7 years, except during a two-month period of each year, a period that happened to include her birthday. Therefore her consumption levels are shown in Figure IX.A-3 below for ages 3.5 years, 4.5 years, etc.

The levels of goat's milk and milk product consumption reported by CATI respondents for these 46 participants ranged up to six 8 oz. servings per day for both women and men.

Figure IX.A-3. Goat's Milk Consumption, by Sex and Age

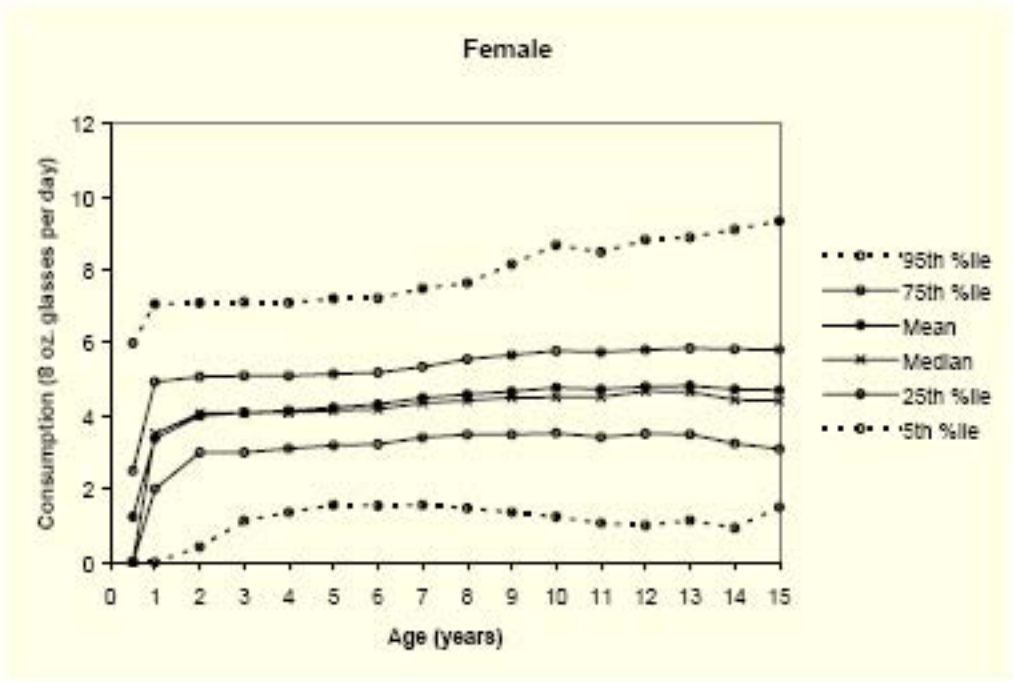


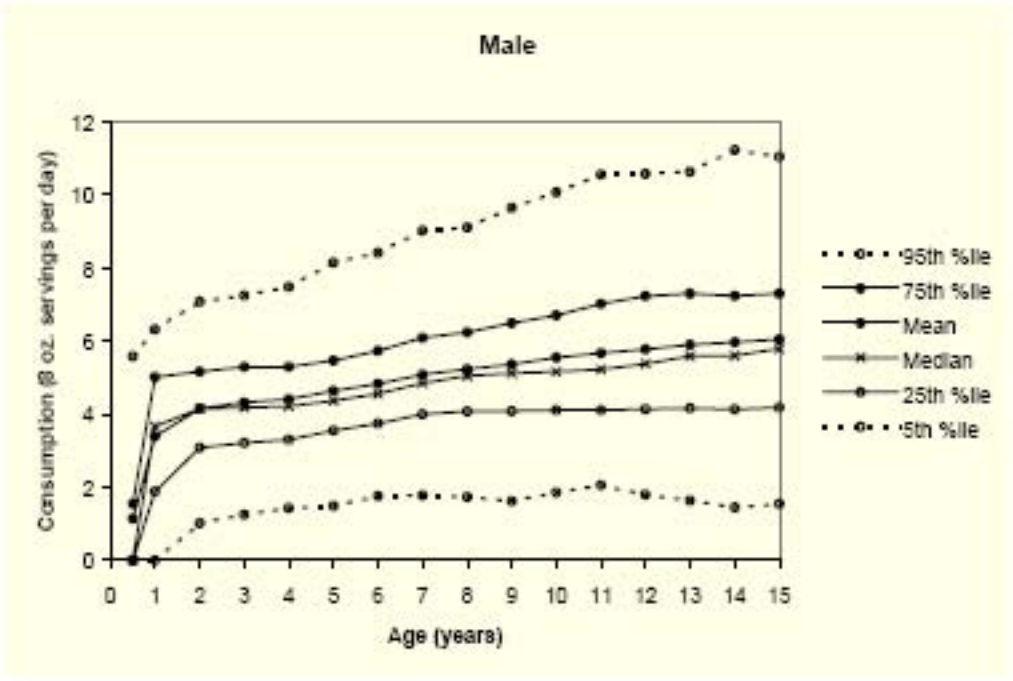
A.6.d. Total Milk and Milk Products

Figure IX.A-4 summarizes the distributions of total milk consumption (raw or processed cow's or goat's milk and milk products) by sex and age. Each participant's consumption, expressed as 8 oz. servings per day, was calculated from that reported for glasses of milk, other servings of milk, and milk products.

As shown in Figure IX.A-4, the reported consumption of milk and milk products increased to about four 8 oz. servings per day at two years of age. For women, consumption remained fairly stable, increasing slightly and gradually until the teenage years. For men, consumption increased steadily up to about six 8 oz. servings per day by age 15. For both sexes, the proportion for whom no milk consumption was reported was 69% at age 6 months and 15% at one year of age. For women, the proportion of nonconsumers fell to 3% at age 2 years, and was 2% or less for all older ages. For men, the proportion of nonconsumers was about 1% at 2 and 3 years of age, and 0.3% or less for all older ages.

Figure IX.A-4. Total Milk Consumption, by Sex and Age



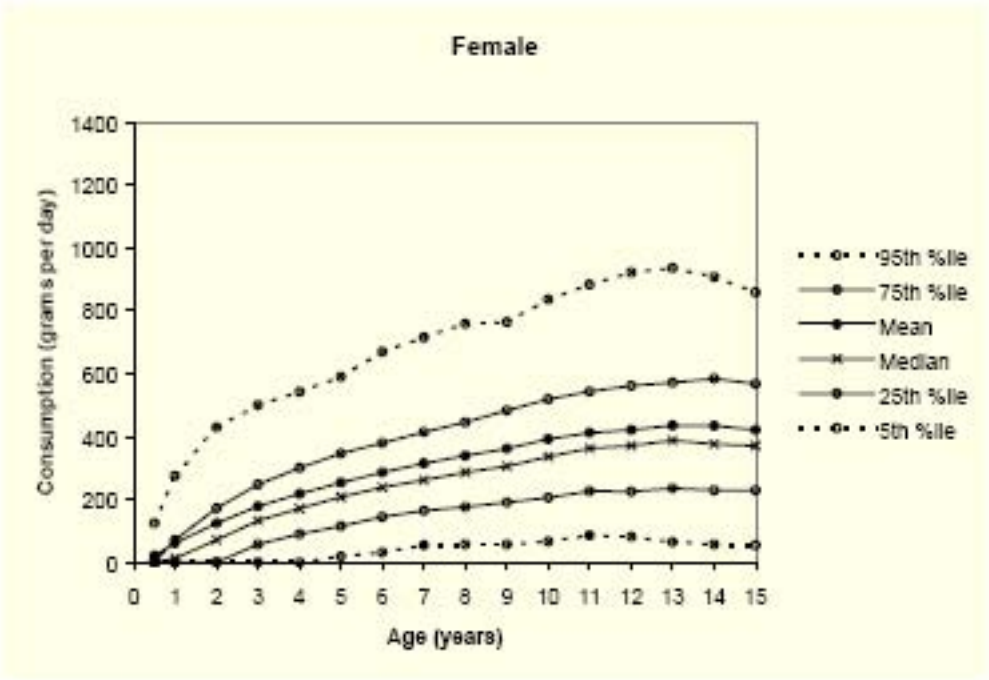


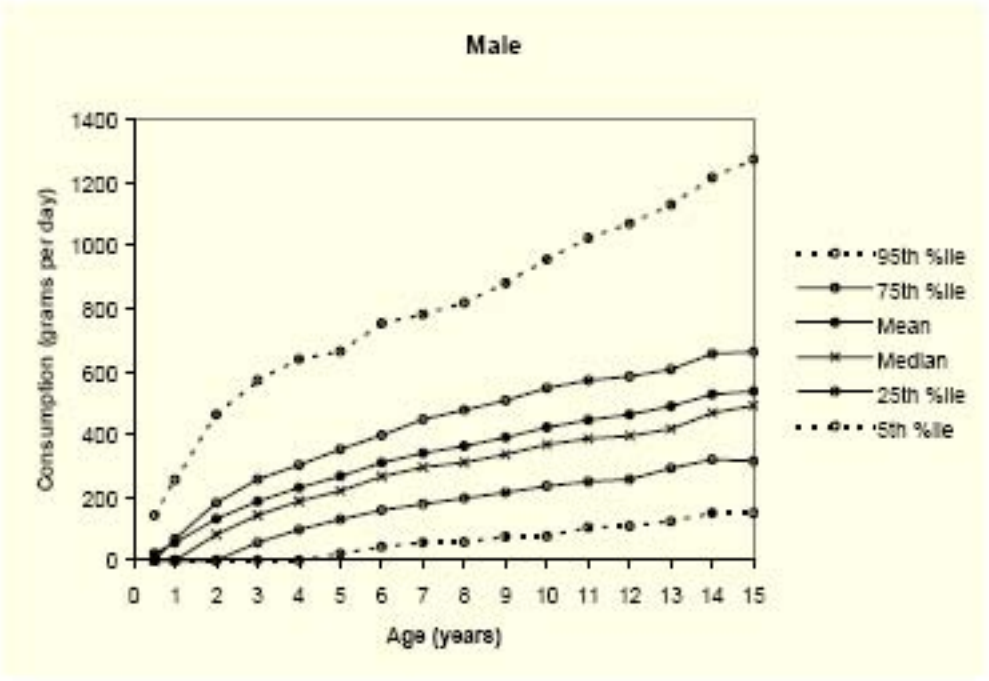
A.6.e. Fruit

Consumption of fruit was reported for 1786 (90.2%) of the 1979 living evaluable in-area participants whose CATI data were used for dose estimation (895 women, 891 men). For 144 of these 1786 (67 women, 77 men), the CATI respondent was unable to provide estimates of the quantities consumed. Figure IX.A-5 summarizes the distributions of fruit consumption by sex and age. Each participant's consumption, expressed as grams per day, was calculated from the information reported by the CATI respondent.

As shown in Figure IX.A-5, the reported consumption of fruit increased steadily with age for both sexes, to about 430 grams per day for women and over 535 grams per day for men by the teenage years. For both sexes, the proportion who were reported not to consume fruit decreased from about 75% at 6 months of age to about 50% and 25% at one and two years of age, respectively. The proportions continued to decrease with increasing age, reaching plateaus of about 2% for women and 1% or less for men after age 7.

Figure IX.A-5. Fruit Consumption, by Sex and Age



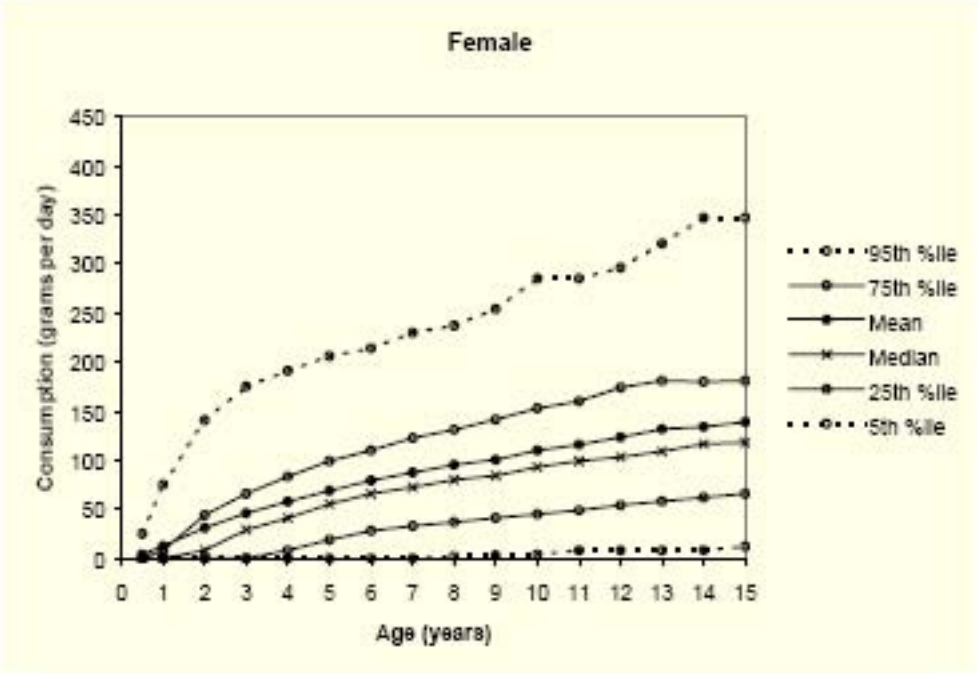


A.6.f. Vegetables

Consumption of green and leafy vegetables was reported for 1693 (85.6%) of the 1979 living evaluable in-area participants whose CATI data were used for dose estimation (855 women, 838 men). For 154 of these 1693 (74 women, 80 men), the CATI respondent was unable to provide estimates of the quantities consumed. Figure IX.A-6 summarizes the distributions of vegetable consumption by sex and age. Each participant's consumption, expressed as grams per day, was calculated from the information reported by the CATI respondent.

As shown in Figure IX.A-6, the reported consumption of vegetables increased steadily with age for both sexes, to about 130 grams per day for women and over 150 grams per day for men by the teenage years. For both sexes, the proportion who were reported not to consume vegetables decreased from over 90% at 6 months of age to 9% at 6 years of age. The proportions of nonconsumers continued to decrease slightly at older ages, ranging between 2% and 4% after age 9.

Figure IX.A-6. Vegetable Consumption, by Sex and Age

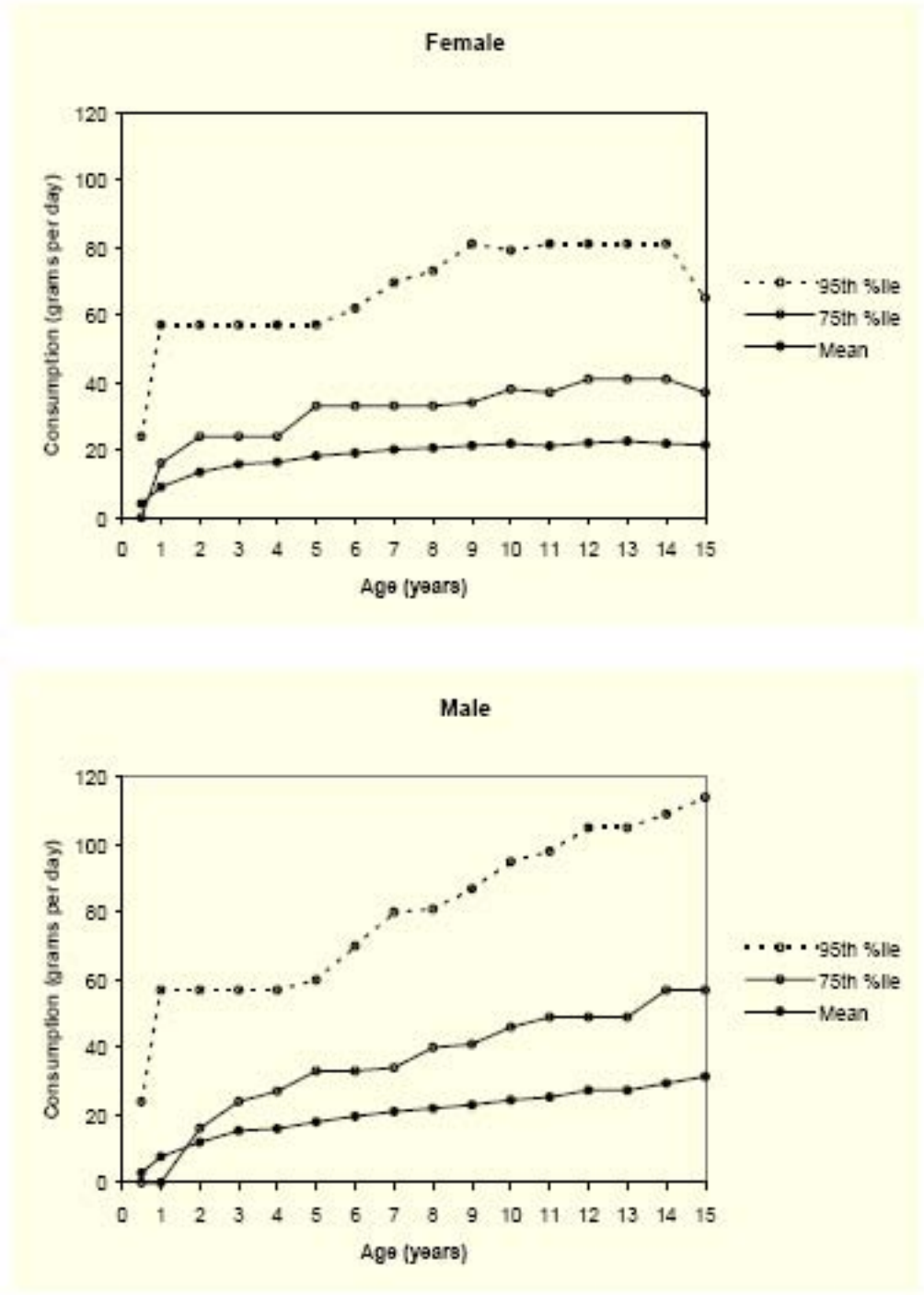


A.6.g. Free Range Chicken Eggs

Consumption of free range chickens was reported for 1057 (53.4%) of the 1979 living evaluable in-area participants whose CATI data were used for dose estimation (552 women, 505 men). For 64 of these 1057 (34 women, 30 men), the CATI respondent was unable to provide estimates of the quantities consumed. Figure IX.A-7 summarizes the distributions of free range chicken egg consumption by sex and age. Each participant's consumption, expressed as grams per day, was calculated from the information reported by the CATI respondent. At every age shown in the figures, fewer than half of the participants were reported to consume free range chicken eggs, and the 5th and 25th percentiles and medians were consequently all zero; therefore these three statistics are omitted from the figure for clarity.

As shown in Figure IX.A-7, the reported consumption of free range chicken eggs increased steadily with age for men, but less so for women. For women, consumption increased to about 16 grams per day by age 3, then increased only slowly to about 22 grams per day by the teenage years. For men consumption increased to about 15 grams per day by age 3, and then continued to increase to about 30 grams per day by the teenage years. For both sexes, the proportion who were reported not to consume free range chicken eggs decreased from over 85% at 6 months of age to just over 50% at 5 years of age, and remained between 50% and 57% for all older ages.

Figure IX.A-7. Free Range Chicken Egg Consumption, by Sex and Age



A.7. Age Distribution for the Alternative Representations to Exposure

As described in section VIII.B.3.b, two alternative representations of exposure to Hanford's ^{131}I were defined, in order to assess whether there might be evidence of a radiation effect that was not apparent from the dose-response analyses using the individual dose estimates calculated by the CIDER program. These alternative representations of exposure were categorical variables, specifically the geostratum and a dichotomous variable defined to identify participants likely to have relatively high versus relatively low exposures (see section VIII.B.3.b.2). Since 1) the definitions of these alternative representations were based entirely (geostratum) or partially (dichotomous exposure variable) on geostratum, and 2) both years of birth and years during which HTDS examinations were performed varied by geostratum, it was of interest to examine whether the participants' ages at HTDS examination were correlated with either alternative representation of dose. Table IX.A-8 shows that the age at HTDS examination varies somewhat by geostratum, with mean age ranging from 49 years for the Okanogan and Ferry/Stevens County geostrata, to 53 years for the Adams County geostratum. This reflects the fact that participants in the Okanogan and Ferry/Stevens geostrata were selected only for the Pilot Study phase, while those from Adams County were selected only during the Full Study phase. In addition, the birth years from which participants were selected were 1942-1946 for the Okanogan and Ferry/Stevens geostrata, while for Adams County they were from 1940-1945.

Table IX.A-8. Age at HTDS Examination by Geostratum

Geostratum	No.	Median	Minimum	Maximum	Mean	St. Dev.
Richland	352	51	46	53	50	1.6
Pasco/Kennewick	1009	52	46	57	52	2.1
Walla Walla City	264	50	46	55	50	1.9
Benton Co.	734	52	46	57	52	2.4
Franklin Co.	149	50	45	57	51	3.1
Walla Walla Co.	334	50	46	55	50	1.9
Okanogan Co.	139	49	46	55	49	2.0
Ferry/Stevens Cos.	138	49	46	54	49	1.5
Adams Co.	321	53	50	57	53	1.6

As can be seen in Table IX.A-9, the age at HTDS examination also differed slightly by the dichotomous exposure variable, with the mean age at HTDS examination 2 years higher in the high exposure group compared to the low exposure group.

Table IX.A-9. Age at HTDS Examination by Dichotomous Exposure Variable

Exposure Group	No.	Median	Minimum	Maximum	Mean	St. Dev.
Low	677	50	46	57	50	2.7
High	580	52	47	57	52	2.0

Although the two tables above indicate that the geostrata, as well as the high and low exposure groups, differed somewhat with respect to the distributions of age at HTDS examination, the differences are rather small, with a maximum difference of 4 years in average age. Although cumulative incidence of disease outcomes or prevalence of thyroid UDAs is likely to increase with age, differences of only a few years of age are unlikely to cause large increases. Nevertheless, the analyses of disease outcomes and thyroid UDAs in relation to these two alternative representations of exposure were adjusted for age at HTDS examination.

B. Estimated Radiation Doses to the Thyroid from Hanford ^{131}I

As described in section VI above, estimates of thyroid radiation doses from atmospheric releases of Hanford's ^{131}I were calculated using the computer program CIDER, which was developed by the HEDR Project (25). Specifically, CIDER calculated estimates of doses received by an individual during any times from December 1944 to the end of 1957, that he or she reports being inside the 246-by-306 mile HEDR geographical domain (Figure II.A-1).

It is important to understand that CIDER does not calculate any contribution to a person's dose for periods he or she reports being outside the HEDR domain. This does not reflect an assumption that persons were not exposed while outside the domain, but rather the difficulty of accurately estimating doses received at long distances from Hanford, and the likelihood that such doses were small. A fundamental objective of the HEDR project in determining the domain's boundaries was to ensure a high likelihood that individuals could not receive appreciable doses while outside the domain. In particular, the domain was defined by the HEDR Project to include as much as possible of the region over which appreciable doses might have been received, while taking into account the decreasing reliability of ^{131}I atmospheric transport modeling at longer and longer distances.

Based on the residence histories obtained from the CATIs and Expanded In-Person Interviews, 3191 (93%) of the 3440 living evaluable participants lived within the HEDR domain at least some time from December 1944 to the end of 1957. These are the participants for whom CIDER can compute a dose estimate. For convenience, these 3191 participants are designated as "in-area" participants in this report (see Table IX.B-1 below). The residence histories of the remaining 249 living evaluable participants (7% of the 3440) included no residence within the HEDR domain from December 1944 to the end of 1957. These 249 individuals are designated as "out-of-area" participants.

Dosimetric data were obtained from CATIs for 2123 (62%) of the 3440 living evaluable participants, and from Expanded-IPIs for the remaining 1317 (38%).

Table IX.B-1. Summary of Dosimetry Interview Types and In-Area Status of 3440 Living Evaluable Participants

	In-Area Status		
Type of Dosimetry Interview	In-Area	Out-of-Area	Total
CATI	1979	144	2123
Expanded In-Person	1212	105	1317
Total	3191	249	3440

B.1. Calculation of Estimated Thyroid Radiation Doses for In-Area Participants

Three sets of dose estimates were calculated for the 3191 in-area participants. The sources of data used for these three sets of doses are summarized in Table IX.B-2.

Table IX.B-2. Characteristics of Primary and Alternative Sets of Radiation Dose Estimates

	Primary Dose Estimates	First Alternative Dose Estimates	Second Alternative Dose Estimates
Use CATI specifics regarding amounts and sources of food and milk?	Yes	No	Yes
Source of default values	HEDR	HEDR	HTDS*

* Note that for expanded IPIs HEDR defaults were used for consumption other than milk.

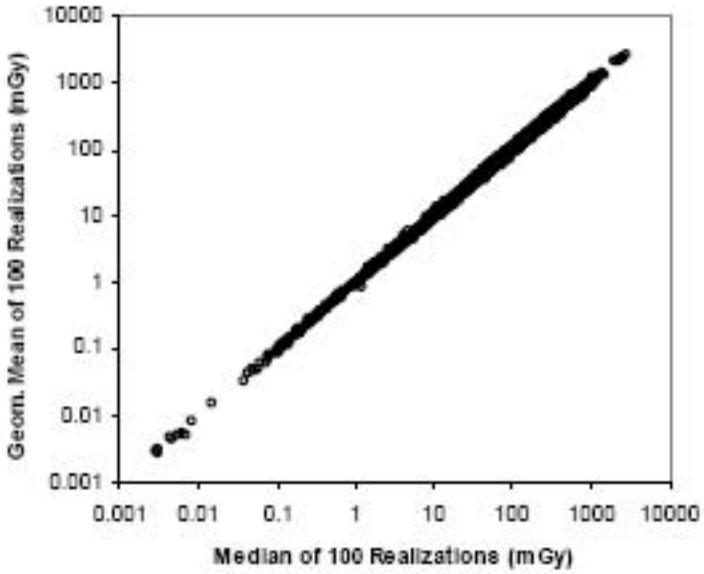
In the dose-response analyses reported below, the primary emphasis is given to results based on the primary set of dose estimates. Analyses using the alternative sets of dose were performed primarily to assess the sensitivity of the dose-response results to the type of dose estimate.

B.2. Point Estimates and Uncertainty of Doses

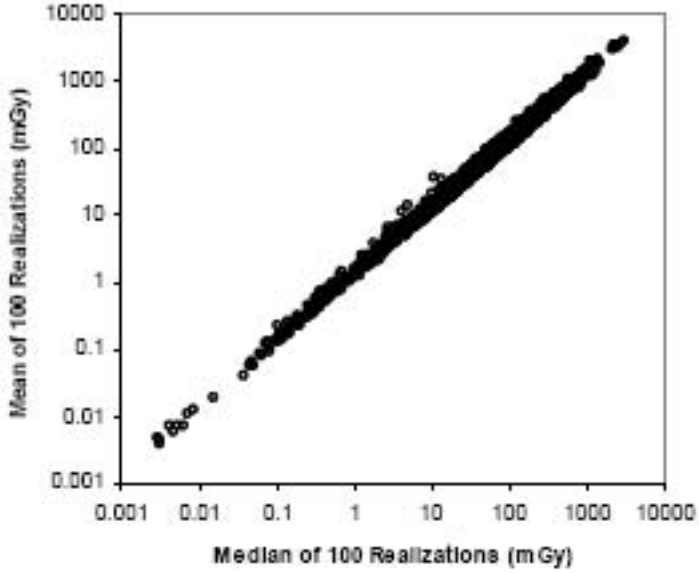
As described in section VIII.B.3.a above, the CIDER program actually returns 100 estimates or "realizations" of each participant's dose. For many purposes, in particular for the conventional analyses of dose-responses described in section VIII.B.3.a above, it is important to have a single number or "point estimate" to serve as each participant's estimated dose. Three obvious candidates for the point estimate are the median, mean, and geometric mean of the 100 realizations. These three point estimates were calculated for each of the 3191 in-area living evaluable participants. It was expected that the three point estimates would be highly correlated with each other, and this is confirmed in Figure IX.B-1 below.

Figure IX.B-1. Scatterplots of Geometric Mean and Mean Doses versus Median Dose

A. Geometric Mean versus Median



B. Mean versus Median

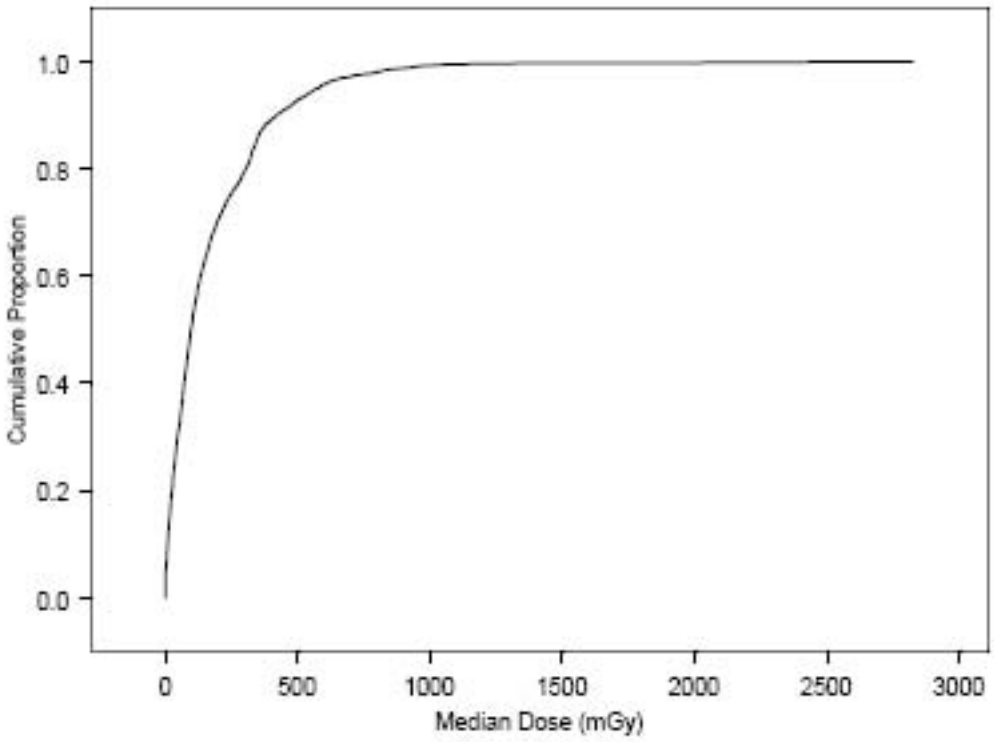


The distributions of each participant's 100 dose estimates tended to be roughly lognormally distributed. Therefore the medians and geometric means were nearly equal for most participants, as can be seen in Panel A of Figure IX.B-1. Furthermore, due to the approximate lognormality of each participant's 100 realizations, the mean doses tended to be somewhat larger than the medians (Figure IX.B-1, Panel B).

Because of the very high degree of correlation among the three possible point estimates, it can be expected that they will give very similar results in the analyses of radiation dose-responses, at least in terms of statistical significance. Therefore the remainder of this report focuses primarily on the median as the point estimate of participants' doses. For simplicity, the terms "doses" or "estimated doses" will refer to the median dose estimates unless otherwise indicated.

Figure IX.B-2 displays the cumulative frequency distribution (CDF) of the median doses. The shape of the CDF indicates that the distribution of median doses is strongly skewed to the right. The majority of participants have relatively low doses, while the rest have doses that are spread over a wide range of higher values.

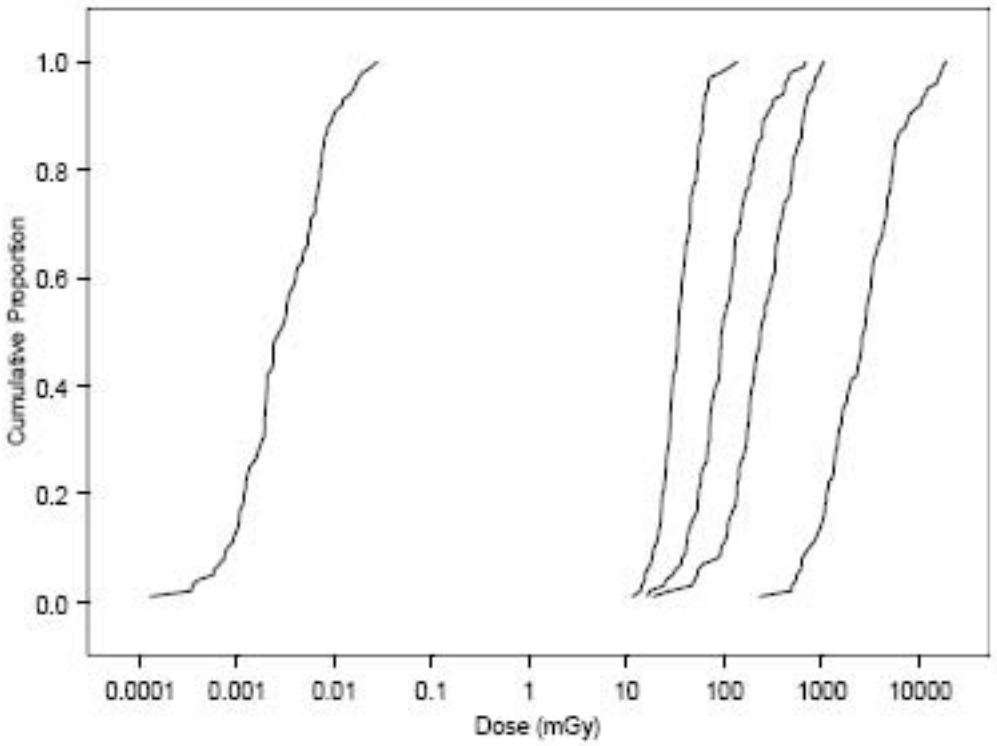
Figure IX.B-2. Cumulative Distribution of Median Dose Estimates for 3191 In-Area Living Evaluable Participants



The uncertainty in each participant's dose estimate is represented by the variation among his or her 100 dose estimates provided by CIDER (see section VIII.B.3.a above). This is illustrated in Figure IX.B-3. Empirical cumulative distribution functions of the 100 dose realizations for each of five selected participants are shown in the figure. The five participants were chosen on the basis of their estimated doses (i.e., the medians of their 100 dose realizations) to cover the entire range of dose estimates. Specifically, the participants in the figure are those with (from left to right) the smallest dose, the 25th, 50th, and 75th

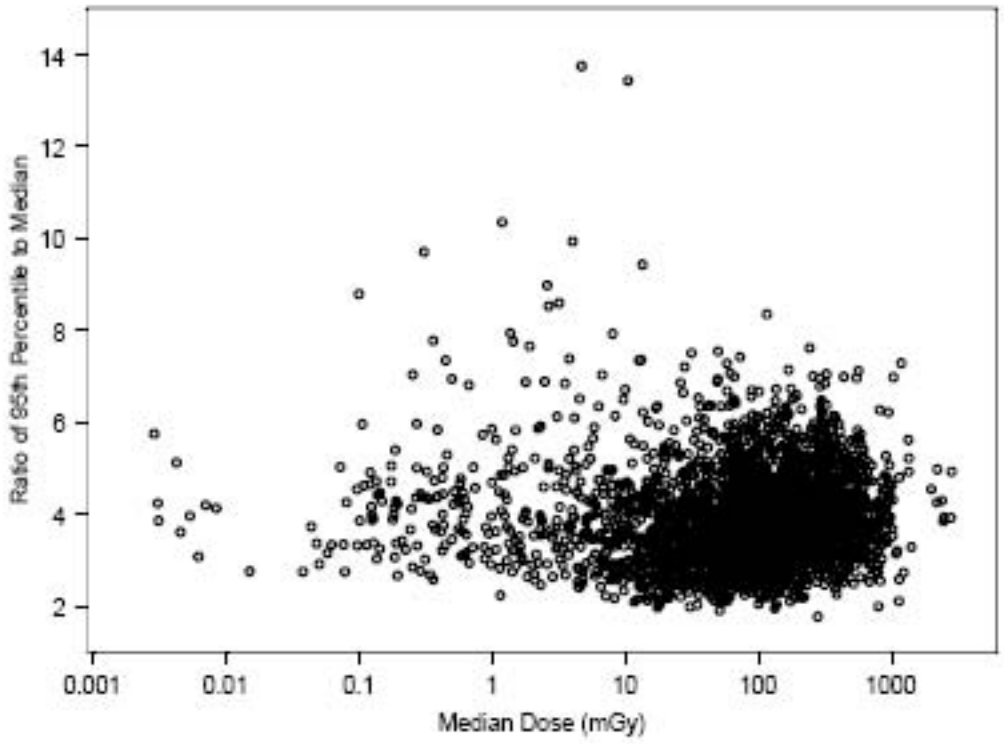
percentile doses, and the largest dose among all 3191 living evaluable in-area participants. It is evident from Figure IX.B-3 that the distributions of 100 realizations are approximately normally distributed. Moreover, the fact that the curves are approximately parallel suggests that the variances of log-transformed dose realizations, or equivalently, the geometric standard deviations of the dose realizations, are roughly the same for each participant.

Figure IX.B-3. Cumulative Distribution of 100 Dose Estimates for Five Selected Participants



One simple and useful characterization of the magnitude of the uncertainty is the ratio of an upper percentile of the 100 realizations, e.g., the 95th percentile, to the median. Among the 3191 in-area living evaluable participants, these ratios had a median value of 3.8 and ranged from 1.8 to 13.7, although the ratio was less than 10.0 for all but three of the 3191 participants. Only 10% of the ratios were less than 2.7, and only another 10% were greater than 5.3. Figure IX.B-4 displays these ratios in relation to the median dose estimates.

Figure IX.B-4. Scatterplot of Ratio of 95th Percentile to Median versus Median Dose



The clustering of the ratios around a value of about 4 is evident in Figure IX.B-4, and there is no indication that the magnitude of uncertainty varies in relation to the median dose.

Another simple characterization of the magnitude of the uncertainties of the estimated doses is the geometric standard deviation or GSD (see section VIII.B.3.a above). For the 3191 living evaluable in-area participants, i.e., the study participants for whom the CIDER program was able to calculate dose estimates, the GSDs ranged from 1.56 to 5.42, with a mean of 2.18.

A total of 890 living evaluable in-area participants (28%) had dose estimates with GSDs less than 2.0. In its review of the HTDS Draft Final Report, the National Research Council (NRC) questioned how GSDs less than 2 could occur, reasoning as follows (159). In CIDER's dose calculations, dose conversion factors (DCFs) were treated as uncertain parameters. For example, CIDER uses age-specific ingestion DCFs to convert total ingested Curies of ^{131}I activity (from milk, food, etc.) into dose (measured in mGy). Similarly, CIDER uses age-specific inhalation DCFs to convert inhaled ^{131}I activity to dose. In CIDER, the DCFs for the ingestion and inhalation pathways, which accounted for most of the dose received by the majority of study participants, were assumed to be lognormally distributed with a GSD of 2.0 (161). Since the GSD of the product of two uncertain variables is the product of their respective GSDs, the NRC reasoned, the GSDs of the doses should rarely if ever be less than 2. The NRC further noted that only GSDs of 2 or greater were reported for representative dose calculations performed by the HEDR project (159).

The NRC failed to recognize that dose estimates with GSDs less than 2.0 were a predictable consequence of the fact that CIDER's calculation of doses involves addition of doses after activity levels are multiplied by DCFs. Specifically, the last step of CIDER's dose calculation is the addition of estimated doses from multiple pathways (ingestion, inhalation, and immersion) and time periods defined by age

and/or calendar year. Each of the estimated dose components in this addition has its own uncertainty, with GSD 2 or greater for ingestion or inhalation components. Now consider the addition of two lognormally distributed (or approximately lognormally distributed) variables with similar GSDs. If the first variable has a much larger geometric mean than the second, the GSD of the sum will generally be close in value to the GSD of the first variable. However if the two variables have similar geometric means, the GSD of their sum will be substantially less than either variable's GSD. Both of these situations occurred in the calculation of dose estimates for the various HTDS participants. Many participants received a large majority of their accumulated dose from one pathway (e.g., ingestion) and one time period (e.g., all or part of 1945). For such participants, the GSD of the total dose was therefore close to the GSD of that dominant component, i.e., 2 or greater. However, for other participants there were two or more components of dose having roughly similar geometric means. When added together, these produced total doses with GSDs less than 2. The NRC also failed to recognize that the representative dose calculations reported by the HEDR project were not informative in this regard. For example, consider the representative doses reported in Table 1 of the paper by Farris et al. (26). The estimated doses for the hypothetical people represented in that table were dominated by the component accumulated through ingestion during 1945. Consequently the GSDs for all of the examples in the table were 2 or greater.

B.3. Distributions of Primary Dose Estimates

The primary estimates of radiation dose for the 3191 in-area living evaluable participants ranged from a minimum of 0.0029 mGy to a maximum of 2823 mGy, with a median of 97 mGy. The mean and standard deviation of the distribution of estimated doses were 174 mGy and 224 mGy, respectively. The distribution of dose estimates was quite heavily skewed, as shown in Figure IX.B-2 above. As shown in Table IX.B-3 below, the distributions of median doses did not differ markedly between women and men.

Table IX.B-3. Frequency Distribution of Estimated Thyroid Radiation Dose, by Sex

Estimated Thyroid Radiation Dose (mGy)	Living Evaluable Participants					
	Female		Male		Total	
	No.	%	No.	%	No.	%
< 10	182	11.2	186	11.9	368	11.5
10-49	320	19.7	314	20.0	634	19.9
50-99	313	19.3	310	19.8	623	19.5
100-149	220	13.6	171	10.9	391	12.3
150-199	126	7.8	109	6.9	235	7.4
200-299	139	8.6	148	9.4	287	9.0
300-399	144	8.9	160	10.2	304	9.5
400-999	171	10.5	154	9.8	325	10.2
1000+	7	0.4	17	1.1	24	0.8
Total In-Area	1622	100	1569	100	3191	100
Out of Area	125	7.2	124	7.3	249	7.2
Total	1747	100	1693	100	3440	100

Twenty-four (0.8%) of the 3191 in-area living evaluable participants had dose estimates greater than 1000 mGy, and only seven (0.2%) had estimates over 2000 mGy. Summary statistics for the distributions of estimated doses are shown by geostratum in Table IX.B-4. As expected, the estimated doses tended to be higher for participants in the Richland, Pasco/Kennewick, and Benton, Franklin and Adams County geostrata. They tended to be lowest for the Okanogan and Ferry/Stevens County geostrata, and intermediate for the two Walla Walla geostrata.

Table IX.B-4. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Geostratum

Geostratum	No.	Median	Minimum	Maximum	Mean	St. Dev.
Richland	348	101	0.1	2455	220	284
Pasco/Kennewick	910	242	.003	1235	255	200
Walla Walla City	250	64	.06	745	74	76
Benton Co.	656	83	.05	2823	170	311
Franklin Co.	141	173	.004	1028	234	215
Walla Walla Co.	320	66	.1	1016	83	93
Okanogan Co.	125	5	.003	158	11	19
Ferry/Stevens Cos.	131	32	.02	128	36	28
Adams Co.	310	161	.008	584	166	101
Total	3191	97	.0029	2823	174	224

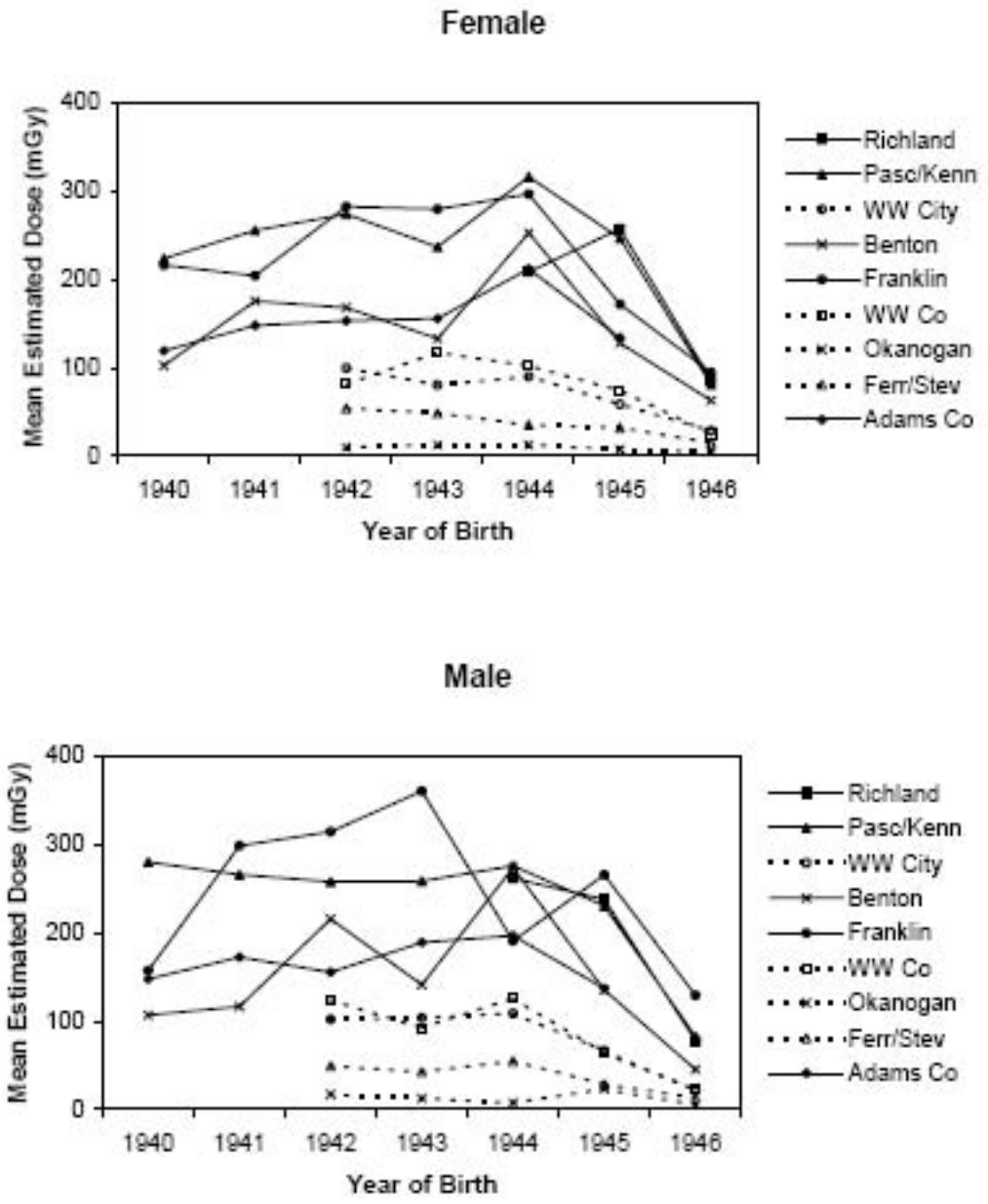
Summary statistics for the distributions of estimated doses are shown by sex and birth year in Table IX.B-5 below. The distributions of estimated doses were similar for men and women. The arithmetic mean doses are slightly larger for men (177 mGy) than women (171 mGy), but the medians are quite similar (96 mGy for men, 99 mGy for women). Seventeen (1.1%) of the 1569 men and 7 (0.4%) of the 1622 women had doses above 1000 mGy. Four of the seven participants with doses over 2000 were female.

Table IX.B-5. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Sex and Year of Birth

Sex	Year	No.	Median	Minimum	Maximum	Mean	St. Dev.
Female	1940	111	122	.04	547	160	132
	1941	133	164	.003	935	202	170
	1942	224	102	.003	952	166	175
	1943	236	102	.007	652	152	146
	1944	416	125	0.05	2823	230	329
	1945	318	94	0.1	956	171	187
	1946	184	29	0.3	373	50	58
	1940-46	1622	99	.003	2823	171	220
Male	1940	107	163	.05	1102	199	187
	1941	122	165	0.3	782	204	163
	1942	211	107	.005	1016	174	166
	1943	248	118	0.2	1235	179	177
	1944	413	114	.003	2455	228	324
	1945	290	73	.08	975	166	208
	1946	178	28	.006	717	48	78
	1940-46	1569	96	.003	2455	177	228
Total	1940-46	3191	97	.0029	2823	174	224

Doses tended to be higher for participants born in 1940 – 1941, to drop somewhat for those born in 1942 – 1943, then to increase again for those born in 1944 . This pattern was largely an artifact of the way in which the study cohort was defined. As described above, the 1940 and 1941 birth cohorts were limited to Benton, Franklin and Adams counties (including Pasco and Kennewick), since these counties were expected to provide participants with relatively high doses. The other counties, from which participants would have been expected to have lower doses, were not included in the 1940 and 1941 cohorts. The effect of this exclusion is shown in Figure IX.B-5 below, which displays the mean estimated doses by sex, birth year, and geostratum.

Figure IX.B-5. Mean of Estimated Median Thyroid Radiation Dose (in mGy) from Hanford ^{131}I by Sex, Year of Birth, and Geostratum



Twenty-three of the 24 participants with estimated doses greater than 1000 mGy were in the Richland, Pasco/Kennewick, Benton or Franklin County geostrata (one was in Walla Walla County). All but three of the 24 were born in 1944, as were all of the seven with estimated doses over 2000 mGy.

Participants' ages at the time of their HTDS examinations ranged from 45 to 57 years. As shown in Table IX.B-6, the participants who were youngest when examined tended to have lower doses, since many of them were born too late to be exposed during the period of highest releases in early and mid 1945.

Table IX.B-6. Summary of Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I by Sex and Age at HTDS Examination

Sex	Age at Exam	No.	Median	Minimum	Maximum	Mean	St. Dev.
Female	45-46*	33	21	0.3	105	34	29
	47	84	35	0.3	472	69	88
	48	136	50	0.1	946	96	137
	49	165	69	0.1	1028	114	147
	50	182	103	0.06	2823	205	320
	51	359	126	0.003	1349	210	220
	52	256	110	0.1	2792	211	296
	53	112	118	0.007	821	169	158
	54	105	163	2.1	676	199	160
	55	133	126	0.004	935	177	161
	56	54	124	0.003	450	146	122
	57	3	128	56	195	126	70
Male	46	26	25	5	717	61	137
	47	106	33	0.006	486	60	79
	48	126	43	0.003	931	104	170
	49	146	69	0.1	1083	138	198
	50	186	80	0.07	1015	168	215
	51	341	120	0.005	2455	220	294
	52	253	120	0.1	1989	214	262
	53	113	171	0.3	1337	216	198
	54	111	168	0.005	782	191	145
	55	107	163	1.4	793	205	179
	56	47	123	0.3	1102	169	188
	57	7	196	.05	368	193	144

* Only one person was 45 years old at the time of examination.

There were two major differences in the dose calculations for participants with CATIs versus those with Expanded In-Person Interviews:

- The first, and perhaps most obvious difference, was the potential availability from CATIs of specific, detailed information about quantities and sources of the milk and other food products consumed by the participant during 1944 – 1957. The CIDER program provided default estimates of these characteristics whenever they were not specified by HTDS. Thus the CIDER defaults were used for all participants with dose calculated from Expanded In-Person Interview. For those with CATI dosimetry data, however, the CIDER defaults were used only when necessary, i.e., when the CATI respondent was unable to provide the information.

- The second major difference between doses calculated from CATI and Expanded In-Person Interview data concerned the contributions to participants' doses from breastfeeding. The CATI included

questions regarding whether or not the participant was breastfed any time after the start of ^{131}I releases from Hanford. However, it was anticipated that many, if not most participants, without CATI respondents would be unable to answer such a question accurately. Therefore the Expanded In-Person Interview did not include questions regarding breastfeeding of the participant. Similarly, since participants without CATI respondents could not be expected to recall details of early life such as the age at which they began drinking cow's milk, no such questions were included in the Expanded In-Person Interview. In the absence of data on these characteristics, the CIDER model assumed that cow's milk consumption began at birth. Therefore all 1212 in-area living evaluable participants with an Expanded In-Person Interview were effectively assumed to have begun drinking cow's milk at birth.

The impact of interview type on the estimated doses is shown in Table IX.B-7.

Table IX.B-7. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Type of Dosimetry Interview and Year of Birth

Interview	Birth Year	No.	Median	Minimum	Maximum	Mean	St. Dev.
CATI	1940	116	150	0.05	1102	209	191
	1941	115	139	1.7	935	208	204
	1942	277	102	0.003	953	173	181
	1943	284	106	0.007	1235	170	184
	1944	511	91	0.003	1143	151	195
	1945	408	59	0.08	943	105	134
	1946	268	29	0.006	717	51	74
	1940-46	1979	81	0.003	1235	140	174
Expanded	1940	102	125	0.04	707	145	112
IPI	1941	139	187	0.003	524	198	128
	1942	158	104	0.06	1016	164	149
	1943	200	106	0.1	498	160	129
	1944	319	247	0.1	2823	355	436
	1945	200	269	0.5	975	299	237
	1946	94	28	1.2	236	46	48
	1940-46	1212	154	0.003	2823	229	279

The average doses (i.e., the means or medians in Table IX.B-7) are generally similar for each year except 1944 and 1945. In those two years, however, the doses based on Expanded In-Person Interviews are notably larger (arithmetic means 355 and 299 mGy, respectively) compared to those based on CATI input data (151 and 105 mGy). This difference reflects the assumption that participants without CATI dosimetry data were assumed to drink cow's milk from birth. As described in the paragraphs above, this likely led to overestimation of the doses for some of the participants with doses based on Expanded In-Person Interviews who were in fact breastfed. In addition, CATI respondents reported that the majority of participants did not consume fresh cow's or goat's milk or milk products in the first months of life (e.g., 69% at 6 months of age; see section IX.A.6.d above).

Table IX.B-8 displays the dose distributions according to age at first exposure to ^{131}I from Hanford, age at HTDS examination, and estimated thyroid dose from the Nevada Test Site (NTS). Participants with prenatal exposure have rather lower doses than other participants, in part since nearly all of the 1946 birth stratum, which missed the months of highest ^{131}I releases from Hanford, were exposed in utero. Participants who were first exposed to ^{131}I from Hanford before 180 days of age also have somewhat lower doses for a similar reason. Participants who were ≤50 years old at the time of their HTDS examinations also had somewhat lower doses, since they tended to be in the later birth year strata. Participants with relatively higher estimated thyroid doses from the NTS tended to have lower doses from

Hanford, in part due to residence. There were no major differences in the doses of those who had a history of any cancer other than thyroid compared to those with no such history.

Table IX.B-8. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Age at Exposure and HTDS Examination, Estimated Thyroid Dose from NTS and History of Any Cancer Other Than Thyroid

Covariate		No.	Median	Minimum	Maximum	Mean	St. Dev.
Prenatal exposure?	Yes	1034	58	.038	2206	135	194
	No	2157	118	.003	2823	193	235
1st exposure before age 180 days?	Yes	1478	75	.038	2823	172	269
	No	1713	115	.003	1350	176	176
Age at HTDS Examination > 50?	Yes	2001	128	.003	2792	203	233
	No	1190	61	.003	2823	125	199
NTS thyroid dose > 5.3 mGy?	Yes	1567	66	.003	2792	128	206
	No	1622	145	.003	2823	218	232
History of any cancer other than thyroid?	Yes	248	104	.003	2823	194	310
	No	2938	96	.003	2792	172	215

Table IX.B-9 displays distributions of estimated dose in relation to participants' histories of various types of medical and dental radiation exposures. The thyroid doses from Hanford do not differ greatly according to the presence or absence of the various kinds of exposure.

Table IX.B-9. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Medical and Dental Radiation History

Have You Ever Had:		No.	Median	Minimum	Maximum	Mean	St. Dev.
CAT scan of the upper body?	Yes	775	98	.003	2823	174	188
	No	2374	96	.003	930	174	236
Diagnostic x-rays of the head?	Yes	1191	90	.003	2482	164	215
	No	1964	102	.003	2823	179	228
Diagnostic x-rays of the neck?	Yes	966	112	.003	2823	195	257
	No	2201	90	.003	2455	164	207
Diagnostic x-rays of the chest or upper? body, including mammograms?	Yes	2821	96	.003	2823	176	228
	No	352	99	.005	1410	161	191
Diag. x-rays of the stomach or mid-back?	Yes	692	96	.003	2482	165	211
	No	2428	97	.003	2823	176	227
Barium enema?	Yes	825	94	.003	2823	174	223
	No	2334	99	.004	2792	174	225
Upper GI?	Yes	1146	99	.003	2823	181	226
	No	2031	96	.004	2792	170	223
Intravenous pyelogram or IVP?	Yes	398	100	.003	1337	185	215
	No	2759	97	.003	2823	172	225
Fluoroscopy of the upper body?	Yes	246	105	.210	1028	192	222
	No	2915	96	.003	2823	172	224
Other nuclear scan?	Yes	217	92	.122	1337	185	219
	No	2945	97	.003	2823	173	225
Radiation treatment for any cancer other than thyroid?	Yes	39	119	.413	1349	202	275
	No	3147	97	.003	2823	174	223
Dental x-rays that did not usually include a lead shield over the neck area?	Yes	1648	95	.003	2482	170	222
	No	1543	99	.005		178	226

Table IX.B-10 displays distributions of estimated dose in relation to participants' occupational histories. The 371 living evaluable in-area participants who reported ever working in a nuclear facility had somewhat higher estimated thyroid doses from Hanford (median 148 mGy).

Table IX.B-10. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Occupational History

Have You Ever Worked in Any of the Following:		No.	Median	Minimum	Maximum	Mean	St. Dev.
Any metal industry?	Yes	238	85	.003	1016	176	204
	No	2953	98	.003	2823	174	226
Any nuclear facility?	Yes	371	148	.015	2455	248	280
	No	2820	93	.003	2823	164	214
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	Yes	442	92	.003	2823	172	258
	No	2749	98	.003	2792	174	218
Any of the above industries or occupations?	Yes	892	104	.003	2823	196	250
	No	2299	94	.003	2792	166	213

As shown in Table IX.B-11, the distributions of estimated thyroid doses from Hanford did not differ appreciably between living evaluable in-area participants who reported any history of smoking cigarettes, or of any smoking, compared to those without such histories.

Table IX.B-11. Summary of Estimated Radiation Doses (in mGy) to the Thyroid from Hanford ^{131}I, by Smoking History

Have You Ever Smoked Any of the Following:		No.	Median	Minimum	Maximum	Mean	St. Dev.
Cigarettes (unfiltered or filtered)?	Yes	1854	96	.003	2823	177	238
	No	1329	98	.005	2206	169	203
Any of cigarettes, cigar or pipe?	Yes	1900	96	.003	2823	177	237
	No	1283	97	.005	2206	169	204

Since the consumption of milk contaminated with ^{131}I from Hanford was a key source of exposure for many study participants, the relationship between milk and milk product consumption and estimated radiation dose was investigated. Average milk and milk product consumption levels (expressed as the reported average number of 8 oz. servings consumed per day) were calculated as described in section VIII.B.2.c above for each of the 1979 living evaluable participants whose CATI data were used for dose estimation. To calculate each participant's average consumption level, his or her reported total number of 8 oz. servings for a particular type of milk was first calculated by integrating the reported consumption levels over the time periods for which the CATI respondent reported consumption levels of that milk. For example, if a CATI respondent reported that a participant consumed three 8 oz. servings per day over a period of 2 years, the total consumption was $3 \times 2 \times 365 = 2190$ 8 oz. servings for that period. For these calculations participants born in 1946 were assigned milk consumption values of 0 for 1945. Also, participants in the 1940-1945 birth strata who never lived inside the HEDR domain during 1945 were assigned consumption levels of 0 for 1945. If the consumption level for a particular type of milk was

unknown for any or all of the time period in question (because the CATI respondent could not report the quantity of glasses consumed), the total consumption was considered unknown for these calculations.

Two measures of average consumption were calculated. The first measure of average consumption, designated "Average No. of 8 oz. Servings per Day," was obtained by dividing the reported total number of 8 oz. servings for a given time period by the duration of that period in days (e.g., by 365 for average consumption during 1945). The second measure, designated "Average No. of 8 oz. Servings per In Area Day," used a different divisor: the number of days during the period for which (1) the participant lived within the HEDR domain and (2) the level of milk consumption was reported in the participant's CATI.

Average consumption levels were calculated for two time periods: (1) 1945, the year in which by far the largest amount of ^{131}I was released from Hanford (see section II above), and (2) the entire period 1944-1957. Table IX.B-12 summarizes milk consumption data reported for the 1979 participants whose CATI data were used for dose estimation are shown for three types of milk: raw ("backyard") cow's milk, processed cow's milk, and goat's milk, as well as for total cow's milk and total milk (cow's plus goat's). Among the 1979 in-area participants whose CATI data were used for dose estimation, the proportions for whom reported average consumption levels were known exceeded 90% for all types of milk. The proportion for whom the reported average consumption level was zero varied widely according to the type of milk or milk product and time period. For example, the proportion with no consumption of cow's milk (raw or processed) was 37% for 1945, but only 8% for all years. This difference reflects the experience of children who were too young to consume cow's milk in 1945, but did consume it at older ages, and the assignment of 0 consumption in 1945 for participants born in 1946. Since very few participants were reported to have consumed goat's milk or milk products, the median consumption levels for these were zero. Similarly the median consumption levels of raw cow's milk and milk products were all 0, since fewer than half of the participants were reported to have consumed these.

Table IX.B-12. Milk and Milk Product Consumption Levels Reported by CATI Respondents: Distributions and Correlation with Estimated Dose

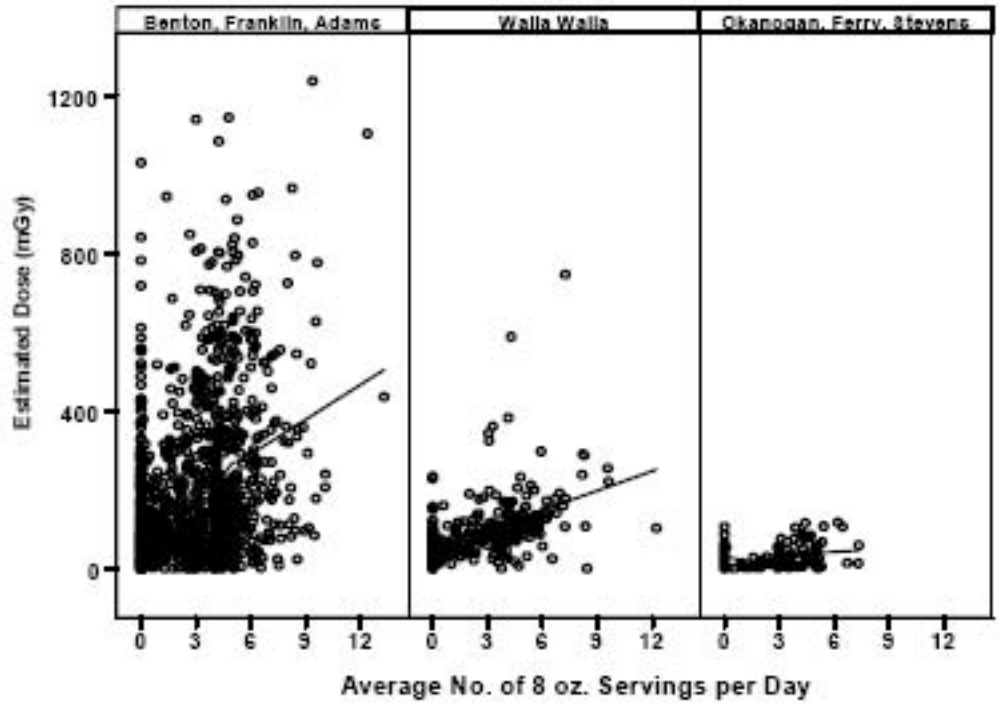
		Participants with Milk and Milk Product Consumption Levels Reported in CATI			Reported Average No. of 8 oz. Servings per Day				Reported Average No. of 8 oz. Servings per In Area Day			
Period	Type of Milk or Milk Product	No.	%	Number (%) with 0	Mean	Median	Range	Corr. with Estimated Dose *	Mean	Median	Range	Corr. with Estimated Dose *
1945	Raw cow's	1927	97%	1351 (70%)	1.05	0	0 – 12.22	0.31	1.09	0	0 – 12.22	0.30
Only	Processed cow's	1904	96%	1016 (53%)	1.07	0	0 – 12.38	0.37	1.19	0	0 – 12.38	0.34
	Total cow's	1866	94%	683 (37%)	2.13	1.37	0 – 12.38	0.57	2.30	1.86	0 – 13.29	0.53
	Goat's	1979	100%	1947 (98%)	0.03	0	0 – 5.69	0.09	0.03	0	0 – 6.00	0.09
	Total	1866	94%	679 (36%)	2.16	1.40	0 – 12.38	0.57	2.33	2.00	0 – 13.29	0.53
1944	Raw cow's	1902	96%	980 (52%)	1.28	0	0 – 11.49	0.23	1.43	0	0 – 11.49	0.21
– 1957	Processed cow's	1854	94%	238 (13%)	2.12	1.66	0 – 12.08	0.31	2.64	2.58	0 – 12.38	0.21
	Total cow's	1807	91%	147 (8%)	3.43	3.58	0 – 12.08	0.46	4.11	4.18	0 – 12.93	0.38
	Goat's	1979	100%	1933 (98%)	0.01	0	0 – 4.29	0.06	0.02	0	0 – 5.00	0.06
	Total	1807	91%	147 (8%)	3.44	3.59	0 – 15.87	0.46	4.12	4.18	0 – 15.87	0.39

* Spearman rank order correlation coefficient

Table IX.B-12 above also shows the correlation between estimated radiation dose and the measures of average milk and milk product consumption. The Spearman rank order correlation coefficients ranged from 0.21 to 0.57 for the various measures of cow's milk and milk product consumption. In contrast, the correlations were quite low for goat's milk and milk products: since these were consumed by only a small minority of the participants, most of the variability of the estimated doses occurred among the nonconsumers of goat's milk and milk products, resulting in the low correlation.

In view of the large number of other factors that influenced the participants' doses, the magnitude of the correlations between estimated dose and these aggregate measures of cow's or total milk and milk product consumption is noteworthy. The effect of milk and milk product consumption on estimated doses of course depends on other factors, in particular the participant's residence history. For example the HEDR model implies that consuming an average of one 8 oz. servings per day throughout 1945 resulted in a higher dose for residents of Franklin county (immediately east of the Hanford site) than for, say, Jefferson County, Oregon (in the southwest corner of the HEDR domain). Figure IX.B-6 displays the relationship between estimated thyroid dose and one measure of milk and milk product consumption, the reported average number of 8 oz. servings per in area day of the total of cow's and goat's milk for 1945. In order to display, at least approximately, the effect of residence location on the relationship between consumption and estimated dose, the participants were divided into three groups based on geostratum: Benton, Franklin and Adams counties (including Richland, Pasco and Kennewick); Walla Walla County (including Walla Walla City); and Okanogan, Ferry and Stevens Counties. While a participant's geostratum (i.e., county of mother's usual residence at the participant's birth) does not correspond perfectly to his or her residence history, it provides a reasonable approximation.

Figure IX.B-6. Estimated Dose in Relation to Reported Consumption of Cow's and Goat's Milk and Milk Products During 1945, by Geostratum



Note: Richland and Pasco/Kennewick geostrata are included within "Benton, Franklin, Adams" and Walla Walla city geostratum is included within "Walla Walla".

The curves in Figure IX.B-6 show smoothed estimates of the average doses, as function of the consumption level, for the three groups. A trend of increasing dose with increasing consumption is evident for the figure. Moreover consumption had a stronger effect on dose for participants in the Benton, Franklin and Adams county geostrata, compared to the other two groups. For example, based on the fitted curves in Figure IX.B-6, the average estimated dose for participants in the Benton, Franklin and Adams County geostrata increased from 85 mGy for those with no consumption of cow's or goat's milk or milk products, (i.e., zero 8 oz. servings per in area day) to 219 mGy for those with an average consumption of four 8 oz. servings per in area day. In contrast, for the Walla Walla County geostrata, the mean estimated dose increased from 38 mGy to 119 mGy, while for the Okanogan, Ferry, and Stevens County geostrata, the mean estimated dose increased from 15 mGy for nonconsumers to 36 mGy for those with an average consumption of four 8 oz. servings per in area day.

As described in Section VIII.B.3.b, two alternative representations of exposure to Hanford's ^{131}I were defined, to assess whether there might be evidence of a radiation effect that was not apparent from the dose-response analyses using the individual dose estimates calculated by the CIDER program. These alternative representations of exposure were categorical variables, specifically the geostratum and a dichotomous variable defined to identify participants likely to have relatively high versus relatively low exposures (see section VIII.B.3.b.2). The analyses of disease and thyroid UDA outcomes in relation to these alternative exposure variables did not make use of the estimated doses. Nevertheless it was of interest to examine the distributions of estimated doses within the categories defined by these two variables.

The distributions of estimated doses are shown by geostratum in Table IX.B-4 above, and by the dichotomous exposure variable in Table IX.B-13 below. Note that the low exposure group included the 249 out-of-area participants for whom the CIDER program does not calculate a dose estimate. Therefore the description of the estimated dose distribution for the low exposure group in Table IX.B-13 refers only to the other 428 participants. As expected, estimated doses of participants in the low exposure group were generally lower, with a mean of 23 mGy, compared to the high exposure group with mean 288 mGy.

However there was substantial overlap in the distributions of estimated doses: the maximum estimated dose in the low exposure group was 160 mGy, while the minimum estimated dose in the high exposure group was 12 mGy. This overlap is not surprising, since the dichotomous exposure variable uses only part of the detailed full set of information that enters into CIDER's calculation of individual dose estimates.

Table IX.B-13. Summary of Estimated Radiation Doses (in mGy) to the Thyroid, by Dichotomous Exposure Variable

Exposure Group	No.	Median	Minimum	Maximum	Mean	St. Dev.
Low – in area	428	15	.003	160	23	25
Low – out of area	249	---	---	---	---	---
High	580	224	12	1235	288	214

The remaining 2183 living evaluable participants, who could not be classified into either the low or the high exposure group, and all of whom were among the in-area group, had estimated doses ranging from 0.003 mGy to 2823 mGy, with mean 173 mGy.

B.4 Implications for Statistical Power

The study's statistical power to detect an effect of ^{131}I from Hanford was determined primarily by the number of living evaluable participants and by the mean and variance of their doses. As described in

section V.A above, the final cohort definition was established in order to ensure a high likelihood that there would be a sufficient number of living evaluable participants and a dose distribution with a sufficiently large variance. Since the power to detect a dose-response of a given magnitude depends on the background rates, power was calculated for three exemplary outcomes corresponding to a range of background rates:

- Any Benign Thyroid Nodule, representing outcomes with intermediate background rates (assumed for power calculations to be 0.05 or 5% for women, 0.02 or 2% for men).

- Thyroid Carcinoma, representing outcomes with low background rates (assumed to be 0.007 or 0.7% for women, 0.003 or 0.3% for men).

- Ultrasound Detected Abnormalities, representing outcomes with high background rates (assumed to be 0.40 or 40% for both sexes).

Table IX.B-14 below summarizes the projections that were made for the Full Study cohort based on the results of the Pilot Study, assuming one-sided tests for a positive dose-response (i.e., slope > 0) at critical level $\alpha = 0.05$, and ignoring dose uncertainties. Also shown are the results that were actually obtained.

Table IX.B-14. Comparison of Projected and Obtained Statistical Power

	Projected	Obtained
Number of in-area living evaluable participants	3277	3191
Mean of dose distribution (mGy)	152	174
Variance of dose distribution (mGy^2)	38619	50150
Any benign thyroid nodule (intermediate background rates): power to detect 0.05 per Gy	0.91	0.95
Thyroid carcinoma (low background rates): power to detect 0.025 per Gy	0.93	0.96
UDAs (high background rates): power to detect 0.12 per Gy	0.86	0.92

It should be noted that the projected results assumed that out-of-area participants would be included, while the "Obtained" results are limited to the in-area participants, who were the basis for the primary analyses of the radiation dose-responses. Although the number of in-area living evaluable participants (3191) fell a bit short of the projection, the mean and variance of the dose distribution were larger than projected. As a result, the statistical power exceeded the projections.

As noted in the NRC's review of the draft HTDS Final Report, the uncertainties of the estimated doses could be expected to reduce the study's power from the levels summarized in Table IX.B-14 above (159). While it would be desirable to calculate the study's power with a direct adjustment for the dose uncertainties, this is impractical due to the complex nature of the correlations of the uncertainties between individual participants. Therefore, in order to assess the impact of dose uncertainty on the study's statistical power, a simulation analysis was performed. Such simulation studies are often used to investigate statistical power when exact calculations are impractical. The basic idea is to randomly generate ("simulate") a large number of data sets that mimic the key characteristics of the study (e.g., background rates, variance of the dose estimates, magnitudes and correlations of the dose uncertainties) for a specific hypothesis (null or alternative). Each simulated data set includes outcome data that are

themselves randomly generated under the hypothesis, and the significance of the resulting dose-response is tested. The proportion of data sets for which the null hypothesis is rejected is then an estimate of the study's power at the specific hypothesis.

For the HTDS, the simulation study began by specifying, for a given exemplary outcome (e.g., any benign thyroid nodule, thyroid carcinoma, or UDA as in Table IX.B-14 above), the sex-specific background rates and the slope of the dose-response under a specific hypothesis of interest (e.g., for any benign thyroid nodule, background rates 0.05 for women and 0.02 for men, and slope 0.05 per Gy). The simulation then proceeded through the following steps:

- Step 1: Randomly select 100 dose realizations with replacement from the existing 100 realizations. (Selection with replacement means that some realizations might not be selected, while others might be selected more than once.) Calculate each participant's median dose from the 100 randomly selected realizations.

- Step 2: Randomly select one of the 100 dose realizations. Treating this single set of doses as the "true" doses, calculate each participant's "true" probability of having the disease outcome using the sex-stratified linear model (see section VIII.C.1.a above) and the specified parameter values. Then randomly generate each participant's disease outcome (present or absent), with the probability of having the disease given by his or her "true" probability.

- Step 3: Fit the sex-stratified linear probability model using the median doses from Step 1 and the outcomes from Step 2, and determine whether the estimated slope is significantly greater than 0 at a given critical level (e.g., $\alpha = 0.05$ or 0.10).

After repeating Steps 1 through 3 for a large number of iterations (e.g., 1000), the proportion of iterations for which the estimated slope was significantly greater than 0 was calculated. This proportion is an estimate of the study's statistical power, i.e., of the probability of rejecting the null hypothesis that the slope is 0.

Note that the random selection with replacement in step 1 was used to ensure that this procedure accounted properly for not only the magnitude of the dose uncertainties, but for the between-participant correlations of dose uncertainties as well.

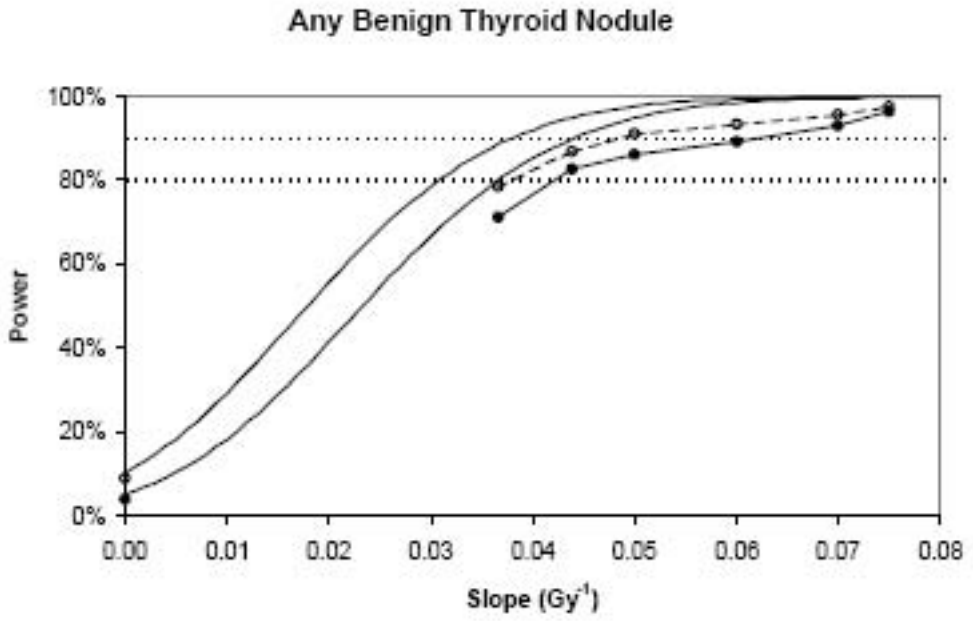
The results of the simulation study for the outcome of any benign thyroid nodule are shown in Table IX.B-15 and Figure IX.B-7. The power was evaluated for the following values of the slope parameter: 0 (i.e., the null hypothesis); 0.036 and 0.044 per Gy, for which the test at critical level $\alpha = 0.05$ has power 0.80 and 0.90, respectively, if dose uncertainty is ignored; and 0.05, 0.06, 0.07, and 0.75 per Gy. Background rates were assumed to be 0.05 for women and 0.02 for men. As expected, the dose uncertainties had no evident effect on the size of the test, i.e., the power under the null hypothesis (slope = 0). In addition, for alternative hypotheses with the slope greater than zero, the simulation study indicated that there was a modest loss of power due to dose uncertainties. For example, if the true slope of the linear dose-response is 0.05 per Gy (5% per Gy), then the estimated power of the test at critical level $\alpha = 0.05$ based on the simulation study (i.e., accounting for dose uncertainties) was 0.863, somewhat less than the value of 0.95 obtained if uncertainty was ignored.

Table IX.B-15. Effect of Dose Uncertainty on Statistical Power: Any Benign Thyroid Nodule

	Power of Test at Critical Level $\alpha = 0.05$		Power of Test at Critical Level $\alpha = 0.10$	
Slope (per Gy)	Ignoring Uncertainty	Accounting for Uncertainty	Ignoring Uncertainty	Accounting for Uncertainty
0	0.05	0.039	0.10	0.090
.036	0.80	0.713	0.88	0.787
.044	0.90	0.829	0.95	0.870
.050	0.95	0.863	0.98	0.912
.060	0.99	0.893	0.99	0.933
.070	0.997	0.931	0.999	0.956
.075	0.999	0.967	1.00	0.978

Although the study was designed to ensure that tests at critical level $\alpha = 0.05$ have adequate power, it should be recognized that dose-response parameters with p-values greater than 0.05 might also be considered evidence of a radiation effect. Therefore results are also shown in Table IX.B-15 for tests at critical level $\alpha = 0.10$. For example, the study had an estimated power of 0.912 for finding a dose-response with p-value < 0.10 if the true dose-response in fact had slope 0.05 per Gy.

Figure IX.B-7. Effect of Dose Uncertainty on Statistical Power: Any Benign Thyroid Nodule



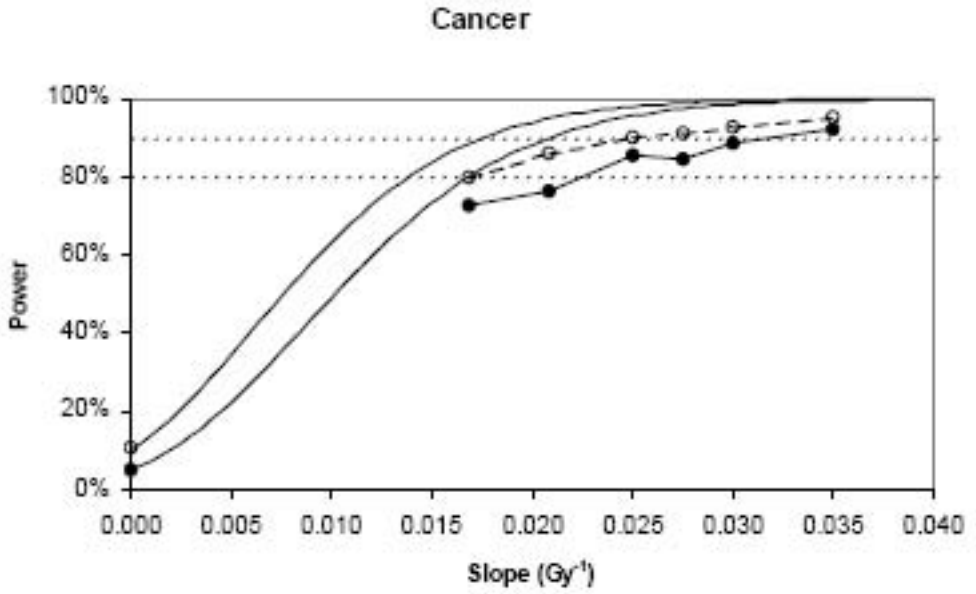
Solid lines show power calculated ignoring dose uncertainties for tests at critical level $\alpha = 0.05$ (lower curve) and 0.10 (upper curve). Circles show estimated power accounting for dose uncertainties, for tests at $\alpha = 0.05$ (solid) and 0.10 (open).

Table IX.B-16 and Figure IX.B-8 display similar results for the outcome of thyroid carcinoma, which represents outcomes with low background rates. The power was evaluated for the following values of the slope parameter: 0 (i.e., the null hypothesis); 0.0169 and 0.0208 per Gy, for which the test at critical level $\alpha = 0.05$ has power 0.80 and 0.90, respectively, if dose uncertainty is ignored; and 0.025, 0.0275, 0.030, and 0.035 per Gy. Background rates were assumed to be 0.007 for women and 0.003 for men. Accounting for dose uncertainties, the power of the test at critical level $\alpha = 0.05$ to detect an effect of 0.025 per Gy (2.5% per Gy) was estimated to be 0.855, compared to 0.96 if uncertainty was ignored.

Table IX.B-16. Effect of Dose Uncertainty on Statistical Power: Thyroid Carcinoma

	Power of Test at Critical Level $\alpha = 0.05$		Power of Test at Critical Level $\alpha = 0.10$	
Slope (per Gy)	Ignoring Uncertainty	Accounting for Uncertainty	Ignoring Uncertainty	Accounting for Uncertainty
0	0.05		0.10	
0.0169	0.80	0.726	0.89	0.799
0.0208	0.90	0.764	0.95	0.864
0.025	0.96	0.855	0.98	0.904
0.0275	0.98	0.848	0.99	0.911
0.030	0.99	0.888	0.995	0.926
0.035	0.996	0.922	0.999	0.952

Figure IX.B-8. Effect of Dose Uncertainty on Statistical Power: Thyroid Carcinoma



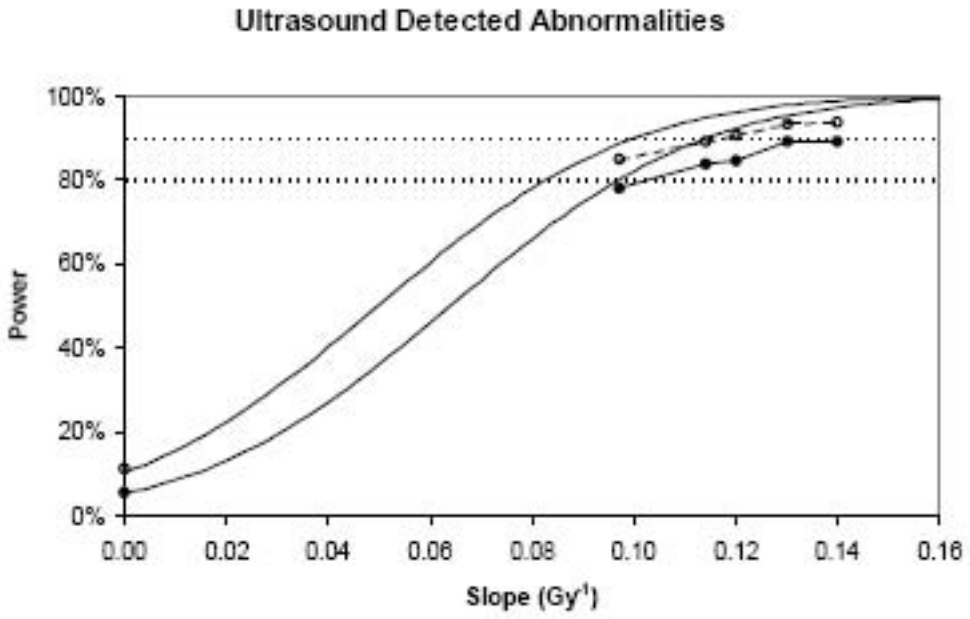
Solid lines show power calculated ignoring dose uncertainties for tests at critical level $\alpha = 0.05$ (lower curve) and 0.10 (upper curve). Circles show estimated power accounting for dose uncertainties, for tests at $\alpha = 0.05$ (solid) and 0.10 (open).

Table IX.B-17 and Figure IX.B-9 display similar results for the outcome of ultrasound detected abnormality, which represents outcomes with high background rates. The power was evaluated for the following values of the slope parameter: 0 (i.e., the null hypothesis); 0.097 and 0.114 per Gy, for which the test at critical level $\alpha = 0.05$ has power 0.80 and 0.90, respectively, if dose uncertainty is ignored; and 0.12, 0.13, and 0.14 per Gy. Background rates were assumed to be 0.40 for both women and men. Accounting for dose uncertainties, the power of the test at critical level $\alpha = 0.05$ to detect an effect of 0.12 per Gy (12% per Gy) was estimated to be 0.847, compared to 0.92 if uncertainty was ignored.

Table IX.B-17. Effect of Dose Uncertainty on Statistical Power: Ultrasound Detected Abnormalities

	Power of Test at Critical Level $\alpha = 0.05$		Power of Test at Critical Level $\alpha = 0.10$	
Slope (per Gy)	Ignoring Uncertainty	Accounting for Uncertainty	Ignoring Uncertainty	Accounting for Uncertainty
0	0.05	0.053	0.10	0.113
0.097	0.80	0.782	0.89	0.852
0.114	0.90	0.840	0.95	0.891
0.12	0.92	0.847	0.98	0.909
0.13	0.95	0.892	0.99	0.936
0.14	0.97	0.894	0.995	0.937

Figure IX.B-9. Effect of Dose Uncertainty on Statistical Power: Ultrasound Detected Abnormalities



Solid lines show power calculated ignoring dose uncertainties for tests at critical level $\alpha = 0.05$ (lower curve) and 0.10 (upper curve). Circles show estimated power accounting for dose uncertainties, for tests at $\alpha = 0.05$ (solid) and 0.10 (open).

In summary, the results of the simulation study showed that the effect of dose uncertainty was, as expected, to reduce the study's statistical power somewhat below the levels calculated with the uncertainties ignored. However, as summarized in Table IX.B-18 below, the reduction was modest, with about 85% power available for the alternative hypotheses to which the study's design was originally targeted.

Table IX.B-18. Summary of Effect of Dose Uncertainties on Statistical Power (one-sided tests at critical level $\alpha = 0.05$)

	Ignoring Uncertainty	Accounting for Uncertainty
Any benign thyroid nodule (intermediate background rates): power to detect 5% per Gy	0.95	0.863
Thyroid carcinoma (low background rates): power to detect 2.5% per Gy	0.96	0.855
UDAs (high background rates): power to detect 12% per Gy	0.92	0.847

To interpret the study's power properly, it is important to consider not only the level of power, but also the size of the dose-response effect for which that power is obtained. For example, for the exemplary outcome with low background rates, thyroid cancer, with assumed background probabilities of 0.7% and 0.3% for women and men, respectively, a linear dose-response with slope 2.5% per Gy yields probabilities of 1.1% and 0.7%, respectively, at the study participants' average dose of 174 mGy. These can also be expressed as relative risks of 1.1/0.7 = 1.62 and 2.45 for women and men, respectively, for an overall

average of 2.04. For the exemplary outcomes with intermediate (any benign thyroid nodule) or high (thyroid UDA) background rates, the corresponding relative risks (average over both sexes) are markedly smaller: 1.30 (5% per Gy) and 1.05 (12% per Gy), respectively. These represent the magnitudes of the effects for which the study's one-sided tests at critical level $\alpha = 0.05$ had estimates of about 85% to 86% power after accounting for the effects of dose uncertainties (see Table IX.B-18 above).

For comparison to results of other studies, the magnitudes of radiation effects can be expressed as the relative risks at 1000 mGy (1 Gy). For the low background rate example of thyroid cancer, a slope of 2.5% per Gy corresponds to probabilities of 3.2% and 2.8% for women and men at 1 Gy, respectively, i.e., to relative risks of 4.57 and 9.33, and an average of 6.95, at 1 Gy. This is similar to the estimated relative risk of 8.9 at 1 Gy reported for the Utah Study in their analysis that did not account for the effects of dose uncertainties (67). However the appropriate comparison is to the estimated relative risk that is obtained after adjusting for the effect of dose uncertainties. The authors of the Utah Study reported that their uncertainty-adjusted estimates were about three-fold greater than the unadjusted estimates, corresponding to a relative risk of $1 + 3 \times (8.9 - 1)$, or about 25 at 1 Gy. A recent analysis suggested that the adjustment should perhaps be smaller: Mallick and colleagues analyzed the Utah Study's data concerning thyroid neoplasms and concluded that the estimated relative risk at 1 Gy should be approximately doubled, rather than tripled, to account for dose uncertainties (165). Assuming this conclusion applies to thyroid cancer, the estimated relative risk would be about 17 at 1 Gy. The HTDS clearly had adequate statistical power to detect an effect of this magnitude. For example, after accounting for dose uncertainty there was an estimated 92% power to detect a linear dose-response with a slope of 3.5% per Gy for thyroid cancer (Table IX.B-18 above), which corresponds to an average relative risk (both sexes combined) of 9.33 at 1 Gy, well below the estimated effect from the Utah Study.

B.5. Out-of-Area Participants

The numbers of out-of-area subjects are shown by sex, birth year, and geostratum in Table IX.B-19. The percentage of out-of-area participants was 7.2% for women (125/1747) and 7.3% for men (124/1693), but varied widely among birth years and geostrata.

Table IX.B-19. Proportions of Out-of-Area Participants, by Sex, Birth Year, and Geostratum

		Living Evaluable Participants	Out-of-Area	
			No.	%
Sex	Female	1747	125	7.2
	Male	1693	124	7.3
Birth Year	1940	243	25	10.3
	1941	283	28	9.9
	1942	472	37	7.8
	1943	560	76	13.6
	1944	906	77	8.5
	1945	611	3	0.5
	1946	365	3	0.8
Geostratum	Richland	352	4	1.1
	Pasco/Kennewick	1009	99	9.8
	Walla Walla City	264	14	5.3
	Benton Co.	734	78	10.6
	Franklin Co.	149	8	5.4
	Walla Walla Co.	334	14	4.2
	Okanogan Co.	139	14	10.1
	Ferry/Stevens Cos.	138	7	5.1
	Adams Co.	321	11	3.4
Total		3440	249	7.2

Only 6 (0.6%) of the 976 participants born in 1945 or 1946 were in the out-of-area group. In the earlier years, however, the percentage ranged from 7.8% (37/472) for 1942 to 13.6% (76/560) for 1943. The sharp drop in 1945-46 reflects that fact that the nearly all participants lived at or near their mother's "usual place of residence" for at least some time after their births. Consequently most participants born in 1945-46 first lived within the HEDR geographical domain. Participants born before 1945 and therefore, for the most part, before the start of ^{131}I releases from Hanford, had more time during which their families might move outside the HEDR domain.

Regarding geostrata, only 4 (1.1%) of the 352 participants in the Richland geostratum were in the out-of-area group. This occurred primarily because Richland was not defined as separate geostratum until 1944. Therefore it does not include participants born during 1940-1943 who, as explained above, had a greater likelihood of moving outside the HEDR domain before the start if Hanford's ^{131}I releases. In the other eight geostrata the percentage of out-of-area participants ranged from 3.4% (11/321) in the Adams County geostratum to 10.6% (78/734) in the Benton County geostratum.

C. Thyroid Cancer

C.1. Occurrence of Thyroid Cancer

The primary and alternative definitions for thyroid cancer were as follows:

- Primary definition: HTDS or prior histologic diagnosis (19 cases)
- Alternative definition: HTDS or prior histologic or clinical diagnosis (20 cases)

Twenty participants (0.6%) were diagnosed with thyroid cancer (Table IX.C-1), including 13 women (0.7%) and 7 men (0.4%). Of the twenty participants found to have thyroid cancer, all but one had diagnoses based on histologic evidence from either the HTDS examination (12) or prior medical care (7). Only one living evaluable participant's diagnosis of thyroid cancer was based on a prior clinical diagnosis. This participant's histology records had been destroyed, but her medical records from 1966 included mention of "Thyroidectomy (cancer) 4/65".

Of the 20 cancer diagnoses, 12 (60%) resulted from the HTDS examination and 8 (40%) were made prior to the participant's HTDS examination.

Table IX.C-1. Diagnoses of Thyroid Cancer, by Basis for Diagnosis and Sex

	Female		Male		Total	
Diagnosis of Thyroid Cancer	No.	%	No.	%	No.	%
Yes	13	0.7	7	0.4	20	0.6
▪ Histologic diagnosis: HTDS	6	0.3	6	0.4	12	0.3
▪ Prior histologic diagnosis	6	0.3	1	0.1	7	0.2
▪ Prior clinical diagnosis	1	0.1	0	--	1	0.0
No	1732	99.1	1685	99.5	3417	99.3
Unknown	2	0.1	1	0.1	3	0.1
Total	1747	100.0	1693	100.0	3440	100.0

Three additional living evaluable participants were classified "unknown" with regard to diagnosis of thyroid cancer. One of these participants had a fine needle aspiration (FNA) prior to the HTDS clinic of a mass outside of the thyroid. This mass was not seen or felt at the HTDS clinic, and no surgery was ever performed, thus thyroid cancer could not be ruled out. The second participant did not have a fine needle aspiration at the HTDS clinic due to a history of cardiac risk, and never had an FNA performed subsequent to the clinic. Again thyroid cancer could not be ruled out. For the third participant the two doctors at the HTDS clinic disagreed as to whether the subject had a lobulation or a small nodule and the ultrasound did not identify any nodules. These three participants were included as non-cases in analyses of the thyroid cancer dose-response.

Three other participants or potential participants had evidence of thyroid cancers that were not included in the primary analysis:

- Two living evaluable participants had thyroid cancers diagnosed after participating in HTDS. In one case the thyroid pathology was incidental to an HTDS recommendation for parathyroid surgery. In the other case the HTDS evaluation concluded that the two palpable nodules at the clinic were most likely non-thyroid, based on a normal nuclear scan. It was subsequently conveyed via a phone call from the participant that she had thyroid cancer. It was determined that since our evaluation of this subject was concluded with no recommendation for surgery or follow-up for definitive pathology, the information from the phone call could not be used or pursued. Although these two diagnoses could not be used in the primary analysis of thyroid cancer, they were included in an additional dose-response analysis (see section IX.C.2.c below).

- One potential participant who refused to participate in HTDS gave as a reason that he/she had thyroid cancer and had already seen too many doctors. Since this person did not participate in the HTDS, this case could not be included in any analyses.

Sixteen (80.0%) of the 20 cancer cases had papillary cancer, while three (15.0%) had follicular cancer (Table IX.C-2). The histologic type was unknown for the one participant with only a prior clinical diagnosis.

Table IX.C-2. Frequency Distribution of Histologic Types of Thyroid Cancer, by Sex

	Female		Male		Total	
Histologic Type	Cases	%	Cases	%	Cases	%
Papillary Cancer	10	76.9	6	85.7	16	80.0
Follicular Cancer	2	15.4	1	14.3	3	15.0
Unknown	1	7.7	0	--	1	5.0
Total	13	100.0	7	100.0	20	100.0

C.1.a Pathways to Diagnosis of Thyroid Cancer

The section above described the sources of information for all diagnoses of thyroid cancer among the living evaluable study participants. The diagnoses that resulted from the HTDS clinical examinations can also be characterized according to the method of detection (or "pathway to diagnosis"). As described in section V.F above, the HTDS employed a comprehensive diagnostic design in which participants received a thyroid ultrasound scan that was viewed only after two independent thyroid physical examinations were conducted by thyroid specialists. Additional thyroid exams were then conducted only if the ultrasound showed abnormalities that were not detected by the physicians. For the 12 diagnoses of thyroid cancer that were made as a result of the HTDS examination, Table IX.C-3 shows which component of the diagnostic process was instrumental in making the diagnosis. The majority of the thyroid cancers (10 or 83%) were detected because one or both of the physicians palpated a new thyroid mass before viewing the videotaped recording of the ultrasound examination. However the other two thyroid cancers were detected only when the physicians repeated the physical examination after reviewing the ultrasound scan. These descriptive results illustrate the contributions of multiple diagnostic methods in the evaluation process. They also underscore the differences that can occur in the prevalence of thyroid disease from one study to another depending on the diagnostic methods used.

Table IX.C–3. Pathways to Diagnosis of Thyroid Cancer

	Thyroid Cancer	
Pathway to Diagnosis	No.	%
Palpable prior to ultrasound	10	83.3
Palpable only after ultrasound	2	16.7
Palpable only (not detected on ultrasound)	0	--
Nonpalpable (detected only on ultrasound)	0	--
Total	12	100

C.2. Analysis of Thyroid Cancer Risk

C.2.a. Primary Analysis

Nineteen living evaluable participants had diagnoses of thyroid cancer based on HTDS or prior histologic evidence. Five of these cases were out-of-area participants, for whom the CIDER program could not calculate dose estimates. The numbers of cases and proportions with thyroid cancer are shown by sex and dose category in Table IX.C-4.

Table IX.C-4. Diagnoses of Thyroid Cancer by Sex, Dose Category, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Prior Histologic Diagnosis		Alternative Definition: Cases Based on HTDS or Prior Histologic or Clinical Diagnosis	
(mGy)	No.	No.	%	No.	%
Out of Area	125	2	1.6	3	2.4
< 10	182	1	0.5	1	0.5
10-49	320	3	0.9	3	0.9
50-99	313	1	0.3	1	0.3
100-149	220	1	0.5	1	0.5
150-199	126	1	0.8	1	0.8
200-299	139	1	0.7	1	0.7
300-399	144	1	0.7	1	0.7
400-999	171	1	0.6	1	0.6
1000+	7	0	--	0	--
Total	1747	12	0.7	13	0.7

B. Male

Thyroid Radiation Dose	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Prior Histologic Diagnosis		Alternative Definition: Cases Based on HTDS or Prior Histologic or Clinical Diagnosis	
(mGy)	No.	No.	%	No.	%
Out of Area	124	3	2.4	3	2.4
< 10	186	1	0.5	1	0.5
10-49	314	2	0.6	2	0.6
50-99	310	0	--	0	--
100-149	171	0	--	0	--
150-199	109	0	--	0	--
200-299	148	0	--	0	--
300-399	160	0	--	0	--
400-999	154	0	--	0	--
1000+	17	1	5.9	1	5.9
Total	1693	7	0.4	7	0.4

The highest estimated dose among the 14 in-area cases was 1083 mGy. Parameter estimates for the linear dose-response model based on the 3191 living evaluable in-area participants are shown in Table IX.C-5 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using primary dose estimates (Table IX.C-5, row 1), the risk of thyroid cancer did not increase

significantly with estimated dose ($p = 0.25$), with an estimated slope B of 0.002 per Gy, and 95% CI ranging from less than −0.001 to 0.017 per Gy. The background thyroid cancer rates were estimated to be 0.006 with confidence interval (0.001, 0.011) for women, and 0.002 with confidence interval (0, 0.005) for men. Results obtained by least squares analysis using ungrouped or grouped data were similar (rows 2 and 3 of Table IX.C-5).

Table IX.C-5. Dose-Response Results for Diagnoses of Thyroid Cancer Based on HTDS or Prior Histologic Evidence

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS or prior, histologic diagnosis)	Linear	Primary	None	MLE	.006 ± .002 (.001, .011)	.002 ± .001 (0*, .005)	.002 ± .004 (< –.001, .017)	0.25
2.	Primary definition	Linear	Primary	None	LSU	.005 ± .002 (.001, .010)	.002 ± .002 (0*, .006)	.005 ± .005 (–.008, .017)	0.19
3.	Primary definition	Linear	Primary	None	LSG	.006 ± .002 (.002, .011)	.003 ± .002 (0*, .007)	–.000 ± .006 (–.015, .014)	0.51
4.	Primary definition	Linear	Primary	+ 2 Incidental cases	MLE	.007 ± .002 (.002, .012)	.002 ± .001 (0*, .005)	.002 ± .004 (< –.001, .017)	0.28
5.	Primary definition	LQ	Primary	None	LSU	.006 ± .002 (.001, .011)	.002 ± .002 (0*, .007)	Lin: .002 ± .009 (–.020, .024) Quad: .002 ± .006 (–.012 .017)	Quad: 0.70

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.C-5. Dose-Response Results for Diagnoses of Thyroid Cancer Based on HTDS or Prior Histologic Evidence (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Primary definition	Logistic	Primary	None	MLE	.005 (.002, .013)	.002 (.001, .008)	.71 ± .79 (-1.18, 2.61)	0.22
7.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.007 ± .002 (.001, .013)	.002 ± .001 (0*, .005)	−.002 ± .006 (NE, >.011)	0.77
8.	Primary definition	Logistic	Primary	Exclude dose > 400 mGy	MLE	.007 ± .003 (0*, .014)	.002 ± .001 (0*, .005)	−.006 ± .016 (NE, .015)	0.87
9.	Primary definition	Linear	Primary	Exclude OK and F/S geostrata	MLE	.006 ± .002 (.0005, .011)	.002 ± .001 (0*, .006)	.002 ± .004 (<-.001,.018)	0.26
10.	Primary definition	Linear	Alt. #1	None	MLE	.006 ± .002 (.001, .012)	.003 ± .002 (0*, .007)	−.001 ± .005 (NE, .015)	0.59

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.C-5. Dose-Response Results for Diagnoses of Thyroid Cancer Based on HTDS or Prior Histologic Evidence (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
11.	Primary definition	Linear	Alt. #2	None	MLE	006 ± .002 (.0005, .012)	.003 ± .001 (0*, .006)	–.001 ± .010 (NE, .008)	0.80
12.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.007 ± .002 (.002, .012)	.004 ± .002 (.0001, .008)	.0006 ± .004 (<-.002, >.015)	0.44
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.007 ± .002 (.002, .012)	.004 ± .002 (.0001, .008)	.0002 ± .004 (<-.002, >.014)	0.48

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

C.2.b. Alternative Definition for Diagnosis of Thyroid Cancer

As described in section IX.C.1 above, only one participant had a diagnosis of thyroid cancer based on anything other than HTDS or prior histologic diagnosis. This case was an out-of-area participant, and therefore had no effect on the primary dose-response analysis.

C.2.c. Effect of Including Incidental Diagnoses of Thyroid Cancer

As described in section IX.C.1 above, two living evaluable participants had thyroid cancers that were determined to be incidental. That is, each diagnosis was made after the participant's HTDS examination, and not as a result of a study recommendation for further evaluation of a possible thyroid cancer. These two cases were not included in the primary analysis of thyroid cancer to avoid introducing a possible reporting bias. However, in view of the importance of thyroid cancer as a disease outcome, additional analyses that included these two incidental cases were performed. These two participants were both in the in-area group, and their estimated thyroid radiation doses were 169 and 62 mGy. When these two incidental cases were included along with the 14 in-area cases in the primary analysis, the results were essentially unchanged, with estimated slope 0.002 per Gy with 95% CI ranging from less than –0.001 to 0.017 per Gy (Table IX.C-5, row 4).

C.2.d. Alternative Dose-Response Functions

Shown in row 5 of Table IX.C-5, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.002 with Bonferroni-adjusted 95% confidence interval ranging from –0.012 to 0.017. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.70$).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.71 with Bonferroni-adjusted 95% confidence interval ranging from –1.18 to 2.61. Thus there was no evidence from the logistic regression model that cumulative incidence of thyroid cancer increased significantly with increasing dose ($p = 0.22$, Table IX.C-5, row 6).

C.2.e. Effect of Excluding Participants in High Dose Categories

The proportions of in-area women with cancer varied little over the dose categories shown in Table IX.C-4, ranging between 0.3% and 0.9%, with no cases among the seven women with doses over 1000 mGy. One of the four male thyroid cancer cases in the in-area group had an estimated dose of 1083 mGy, while the other three had doses less than 50 mGy. Consequently, when participants in the highest dose categories (> 1000 mGy or > 400 mGy) were excluded, the estimated slope of the dose-response decreased slightly, to –0.002 per Gy with Bonferroni-adjusted 95% upper confidence limit exceeding 0.011 per Gy among those with doses < 1000 mGy, and to –0.006 per Gy with upper confidence limit 0.015 per Gy among those with doses < 400 mGy (Table IX.C-5, rows 7 and 8). Thus there was no evidence that the dose-response results were inordinately influenced by the outcomes of participants in the highest dose categories.

C.2.f. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When participants in the Okanogan and Ferry/Stevens geostrata were excluded, the estimated slope of the dose-response changed only slightly, to 0.002 per Gy with 95% CI ranging from less than

–0.001 to 0.018 per Gy (Table IX.C-5, row 9). Thus there was no evidence that the dose-response results were inordinately influenced by the outcomes of participants in these geostrata.

C.2.g. Analysis of Thyroid Cancer in Relation to Alternative Dose Estimates

Parameter estimates for the linear dose-response model using the alternative dose estimates are shown in rows 10 and 11 of Table IX.C-5 above. For both alternative dose estimates the estimated slope B decreased as compared to the primary dose set, from 0.002 to –0.001, and thus in neither case was there evidence that the cumulative incidence of thyroid cancer increased with increasing dose.

C.2.h. Scoping Analyses Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 12 and 13 of Table IX.C-5, in both analyses the inclusion of the out-of-area participants slightly decreased the estimated slope of the dose-response, but did not materially change the dose-response results.

C.2.i. Analysis of Thyroid Cancer in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

C.2.i.1. Analysis by Geostratum

Since only 19 participants had thyroid cancer (see Table IX.C-6), the test for heterogeneity among the nine geostrata had little statistical power. Therefore the absence of significant heterogeneity ($p = 0.73$) was not strong evidence against the possibility that the cumulative incidence of thyroid cancer might in fact vary among the geostrata. The percentages with cancer were somewhat higher in the Okanogan and Ferry/Stevens geostrata (1.4% for women, 0.7% for men) than in the remaining geostrata (0.6% and 0.4%), but this difference was also not statistically significant ($p = 0.26$).

Table IX.C-6. Diagnoses of Thyroid Cancer Based on HTDS or Prior Histologic Evidence, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	1	0.6	173	1	0.6	352	2	0.6
Pasco/Kennewick	508	3	0.6	501	1	0.2	1009	4	0.4
Benton County	376	2	0.5	358	2	0.6	734	4	0.5
Franklin County	73	0	--	76	0	--	149	0	--
Adams County	165	1	0.6	156	0	--	321	1	0.3
Walla Walla (city)	133	1	0.8	131	1	0.8	264	2	0.8
Walla Walla County	170	2	1.2	164	1	0.6	334	3	0.9
Okanogan County	75	1	1.3	64	1	1.6	139	2	1.4
Ferry/Stevens Counties	68	1	1.5	70	0	0.0	138	1	0.7
Total	1747	12	0.7	1693	7	0.4	3440	19	0.6

C.2.i.2. Analysis by Dichotomous Exposure Variable

See section VIII.B.3.b.2 above for a description of the high and low exposure categories. Eleven (0.9%) of the 1257 participants included in these analyses had thyroid cancer based on an HTDS or prior histologic examination (see Table IX.C-7). These included 3/580 (0.5%) in the high exposure group and 8/677 (1.2%) in the low exposure group. Thus there was no evidence that cumulative incidence of thyroid cancer was elevated in the high exposure group (p = 0.86).

Table IX.C-7. Diagnoses of Thyroid Cancer based on HTDS or prior histologic evidence, by exposure group and sex

Exposure	Female			Male			Total		
Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	4	1.1	326	4	1.2	677	8	1.2
High	298	2	0.7	282	1	0.4	580	3	0.5
Total	649	6	0.9	608	5	0.8	1257	11	0.9

C.2.j. Confounding and Effect Modification

There were too few participants with diagnoses of thyroid cancer to warrant any analysis of confounding or effect modification.

C.2.k. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for thyroid cancer are shown in Figure IX.C-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence interval, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 65 of the 100 realizations, the confidence interval includes 0 for all of the 100 realizations. Also shown in Figure IX.C-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response.

Figure IX.C-1. Plot of Estimated Slope by Dose Realization

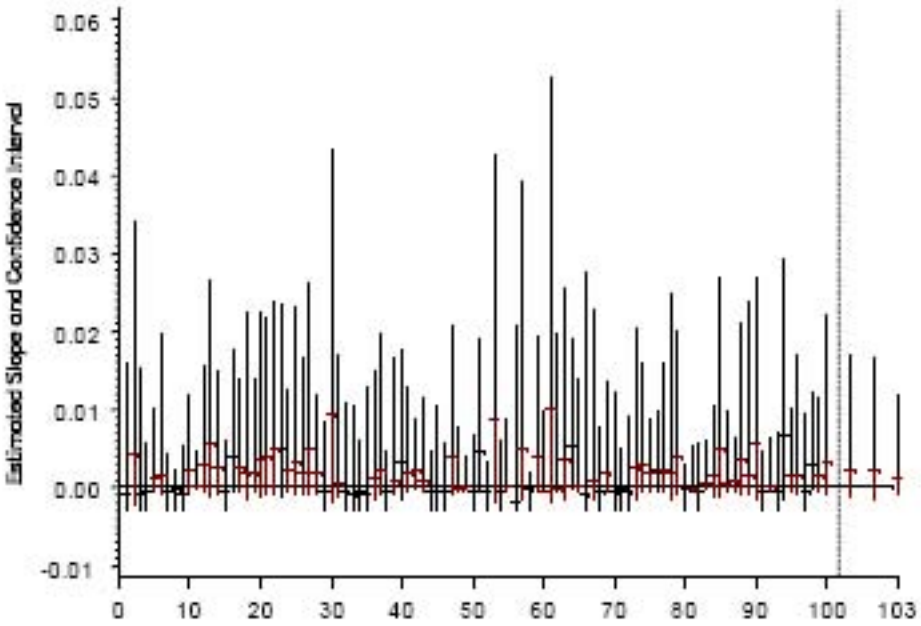
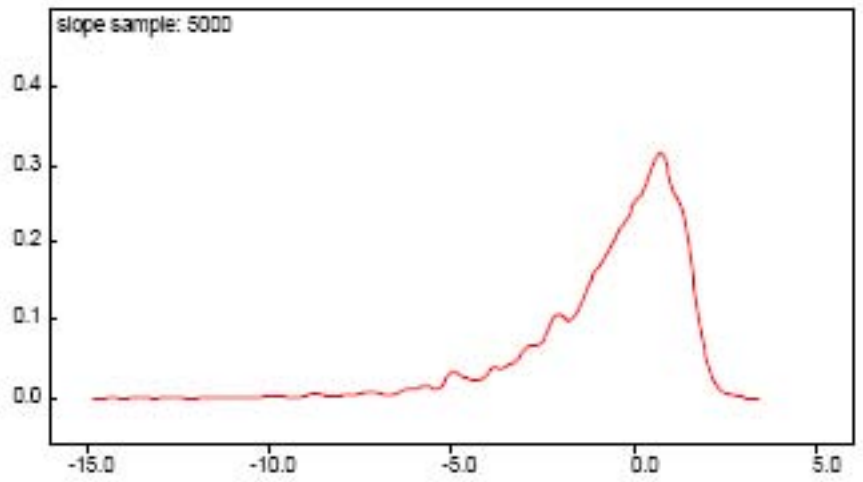


Figure IX.C-2 displays the distribution of the 5000 estimates of the logistic coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –5.0 and 2.0. The estimate was less than or equal to 0 for 2574 of the 5000 replications, implying an empirical one-tailed p-value of 0.52. The median estimate was –0.06, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –8.29 and 2.11. These may be compared to the estimate of 0.71 with confidence interval (-1.18, 2.61) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of thyroid cancer increased with increasing dose.

Figure IX.C-2. Distribution of Simulation Estimates of Logistic Regression Coefficient



D. Benign Thyroid Nodule

D.1. Occurrence of Benign Thyroid Nodule

The primary and alternative definitions for benign thyroid nodule were as follows:

- Primary definition: HTDS or prior, histologic or cytologic diagnosis (249 cases)
- Alternative definition #1: HTDS or prior, histologic, cytologic or clinical diagnosis (287 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (297 cases).

Table IX.D-1 shows the numbers and percentages of living evaluable participants with diagnoses of benign thyroid nodule, and the bases for those diagnoses, by sex. Two hundred and forty-nine (7.2%) living evaluable participants had a diagnosis of benign thyroid nodule based on histologic or cytologic evidence arising from the HTDS examination or from a prior diagnosis, with 170 (9.7%) women 79 (4.7%) men having this condition, respectively. Thirty-eight (1.1%) participants had diagnoses classified as clinical. Additionally, for 10 (0.3%) the diagnosis was based solely on a report by the participant or his/her CATI respondent.

Table IX.D-1. Diagnoses of Benign Thyroid Nodule, by Basis for Diagnosis and Sex

	Female		Male		Total	
Diagnosis of Benign Thyroid Nodule	No.	%	No.	%	No.	%
Yes	200	11.4	97	5.7	297	8.6
▪ Histologic diagnosis: HTDS	7	0.4	6	0.4	13	0.4
▪ Cytologic diagnosis: HTDS	142	8.1	65	3.8	207	6.0
▪ Prior histologic diagnosis	19	1.1	7	0.4	26	0.8
▪ Prior cytologic diagnosis	2	0.1	1	0.1	3	0.1
▪ Clinical diagnosis: HTDS	16	0.9	13	0.8	29	0.8
▪ Prior clinical diagnosis	7	0.4	2	0.1	9	0.3
▪ Participant/respondent report	7	0.4	3	0.2	10	0.3
No	1545	88.4	1595	94.2	3140	91.3
Unknown	2	0.1	1	0.1	3	0.1
Total	1747	100.0	1693	100.0	3440	100.0

Three living evaluable participants were classified "unknown" with regard to diagnosis of benign thyroid nodule. One of these participants reported a history of having a thyroid "lump" removed, but had no record of surgery or evidence of a surgical scar. The second participant's medical record included mention of thyroid nodule by one physician. However a second physician disagreed, revising the diagnosis to thyromegaly, with decrease in size after treatment. For the third participant, the two doctors at the HTDS clinic disagreed as to whether the subject had a lobulation or a small nodule and the ultrasound did not identify any nodules (this participant was also classified as "unknown" for diagnosis of thyroid cancer). These three participants were included as non-cases in analyses of the dose-response for benign thyroid nodule.

As shown in Table IX.D-2, the majority of benign thyroid nodules were colloid nodules (69.7%). Follicular adenomas accounted for only 4.7% of the diagnoses. The remaining 33.0% included a variety of types of nodules, which are described in Table IX.D-3.

Table IX.D-2. Frequency Distribution of Histologic/Cytologic Types of Benign Thyroid Nodule, by Sex

	Female		Male		Total	
Histologic/Cytologic Type	Cases	%	Cases	%	Cases	%
Colloid nodule	139	69.5	68	70.1	207	69.7
Follicular adenoma	8	4.0	6	6.2	14	4.7
Other	71	35.5	26	26.8	97	32.7
Total with benign thyroid nodule	200	100.0	97	100.0	297	100.0

Note: A participant can have >1 histologic/cytologic type

Table IX.D-3. Frequency Distribution of Other Histologic/Cytologic Types of Benign Thyroid Nodule, by Sex

	Female		Male		Total	
Other Histologic/Cytologic Type	Cases	%	Cases	%	Cases	%
Unknown/uncertain*	25	35.2	14	53.8	39	40.2
Hashimoto's thyroiditis	23	32.4	6	23.1	29	29.9
Thyroglossal duct cyst	4	5.6	1	3.8	5	5.2
Adenomatous nodule/goiter	3	4.2	2	7.7	5	5.2
Benign follicular nodule	7	9.9	1	3.8	8	8.2
Benign nodular goiter	2	2.8	0	--	2	2.1
Chronic thyroiditis w/benign follicles & Hurthle cells	1	1.4	0	--	1	1.0
Colloid nodule vs follicular adenoma	1	1.4	0	--	1	1.0
Hashimoto's & non-neoplastic follicular nodule w/colloid	1	1.4	0	--	1	1.0
Nodular hyperplasia	1	1.4	0	--	1	1.0
Possible thyroiditis	1	1.4	0	--	1	1.0
Simple cyst	1	1.4	0	--	1	1.0
Nondiagnostic, probable colloid nodule	1	1.4	0	--	1	1.0
Unknown due to participant/respondent report	0	--	1	3.8	1	1.0
Probable neoplastic macrofollicular nodule	0	--	1	3.8	1	1.0
Total with other histologic/cytologic type	71	100.0	26	100.0	97	100.0

* No cytology available

Of the 98 participants with histologic/cytologic type classified 'Other' (Table IX.D-3), 39 (39.8%) were of unknown or uncertain type, meaning no cytology was available. Another 29 (29.6%) were associated with Hashimoto's thyroiditis, 8 (8.2%) were due to a benign follicular nodule, 5 (5.1%) were due to a thyroglossal duct cyst, 5 (5.1%) were due to an adenomatous nodule, 2 (2.0%) were due to a benign nodular goiter, and the remaining 9 were due to varying individual specifications of the histologic/cytologic type.

D.1.a. Additional Disease Outcomes Related to Benign Thyroid Nodule

The following additional disease outcomes related to benign thyroid nodule were considered. These outcomes were defined based on the primary definition of benign thyroid nodule (i.e. HTDS or prior, histologic or cytologic evidence).

D.1.a.1 Benign Thyroid Nodules and Nodules Suspicious for Thyroid Follicular Adenoma

Additional analyses were performed in which the participants with either benign thyroid nodules or nodules coded as "suspicious for follicular neoplasm" were combined as cases. The category of suspicious for follicular neoplasm deserves some additional comment. Participants having FNA biopsy for a palpable nodule or a nonpalpable nodule larger than an average of 1.5 cm, were recommended to have further evaluation or consideration of thyroid surgery if the FNA result was reported as either suspicious for malignancy or suspicious for follicular neoplasm. For those participants who did have surgery, the HTDS final diagnosis was then designated as either cancer or benign thyroid nodule based on the surgical pathology. However, there were 16 participants with FNA results reported as suspicious for follicular neoplasm who chose not to have surgery. None of those individuals had FNA results that were suspicious for cancer. Their FNA results showed either intermediate or high probability of follicular neoplasm; none were suspicious for papillary cancer. Although these 16 cases were most likely to represent a benign thyroid nodule, the risk of thyroid cancer in such cases has been reported to be approximately 10-30%.

Sixteen participants without other benign thyroid nodules (14 women, 2 men) had diagnoses of nodules suspicious for follicular neoplasm, all based on cytology. Consequently the 3440 living evaluable participants included 265 (7.7%) with diagnoses of benign thyroid nodule or nodule suspicious for follicular neoplasm (Table IX.D-4), with more than twice as many cases among women (10.5%) than men (4.8%).

Table IX.D-4. Benign Thyroid Nodule and Nodules Suspicious for Follicular Neoplasm, by Sex

Benign Thyroid Nodule or Nodule Suspicious for Follicular Neoplasm	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	184	10.5	81	4.8	265	7.7
No	1563	89.5	1612	95.2	3175	92.3
Total	1747	100.0	1693	100.0	3440	100.0

D.1.a.2. Benign Thyroid Nodule Excluding Non-neoplastic Disease

The outcome of benign thyroid nodule excluding non-neoplastic etiology was defined in order to exclude cases that might have a specific non-neoplastic etiology, as their inclusion might mask a dose-response effect. This outcome was defined to include participants with a diagnosis of benign thyroid nodule based on histologic or cytologic evidence from the HTDS or prior examination, but excluding those with any of the following:

- Autoimmune thyroiditis based on HTDS evaluation or medical records with supporting documentation;
- Graves disease based on HTDS evaluation or medical records with supporting documentation; or
- Hyperthyroidism based on HTDS evaluation or medical records with supporting documentation with an etiology of toxic nodular goiter or solitary toxic nodule.

Among the 3440 living evaluable participants 175 (5.1%) had a diagnosis of benign thyroid nodule excluding a non-neoplastic etiology, with the percentage of cases about twice as high for women (6.7%) as for men (3.4%) (Table IX.D-5).

Table IX.D-5. Benign Thyroid Nodule Excluding Non-neoplastic Disease, by Sex

Benign Thyroid Nodule Excluding Non-neoplastic Disease	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	117	6.7	58	3.4	175	5.1
No	1630	93.3	1635	96.6	3265	94.9
Total	1747	100.0	1693	100.0	3440	100.0

D.1.a.3. Solitary Benign Thyroid Nodule Detected without Ultrasound

The outcome of palpable, solitary, benign thyroid nodule detected without ultrasound was defined in order to simulate the effect of screening for thyroid disease by palpation only, i.e., without ultrasound examination. A total of 88 living evaluable participants (64 women, 24 men) had diagnoses of such nodules (Table IX.D-6).

Table IX.D-6. Solitary Benign Thyroid Nodule Detected without Ultrasound, by Sex

Solitary Benign Thyroid Nodule Detected without Ultrasound	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	64	3.7	24	1.4	88	2.6
No	1683	96.3	1669	98.6	3352	97.4
Total	1747	100.0	1693	100.0	3440	100.0

For the majority of the 88 living evaluable participants with solitary benign thyroid nodules that were detected without ultrasound, i.e., by palpation, those nodules were also observed on the ultrasound examination. However for 21 (24%) of the 88, those nodules were not detected by ultrasound. Twelve (57%) of these 21 participants each had 1-6 discrete focal ultrasound abnormalities in addition to the palpable nodule which was not detected on ultrasound. In addition, 15 of 21 (71%) had documented Hashimoto's thyroiditis. Only 4 participants (0.1% of the 3429 living evaluable participants whose thyroid glands were visible in their ultrasound examinations) had a palpable nodule with a completely normal ultrasound scan. These results suggest that the reason for the discordance between palpation and ultrasound in this small group was the abnormal thyroid tissue that is present throughout the gland in individuals with Hashimoto's thyroiditis, a fact well known in clinical practice. Since only 4 participants had true palpable nodules that were not detected by ultrasound, a dose-response analysis of this specific outcome was not feasible.

D.1.a.4. Benign Thyroid Nodule Excluding Colloid-Only Nodules

In the primary analysis, thyroid nodules with abundant colloid but insufficient follicular cells (designated for this study as "colloid-only" nodules) were classified as benign thyroid nodules. Since such a cytology result is technically nondiagnostic, an additional analysis was performed in which the colloid-only nodules were not counted among the benign thyroid nodules. Of the 249 living evaluable participants with diagnoses of benign thyroid nodules, 18 (12 women and six men) had diagnoses based solely on colloid-only nodules. Thus a total of 231 (6.7%) had benign thyroid nodules excluding colloid-only nodules (Table IX.D-7).

Table IX.D-7. Benign Thyroid Nodule Excluding Colloid-Only Nodules, by Sex

Benign Thyroid Nodule Excluding Colloid-only Nodules	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	158	9.0	73	4.3	231	6.7
No	1589	91.0	1620	95.7	3209	93.3
Total	1747	100.0	1693	100.0	3440	100.0

D.1.a.5. Benign Colloid Nodules

Colloid nodules comprised the largest category of benign thyroid nodules. Thus the outcome of benign colloid nodules was defined to determine whether colloid nodules might be related to ^{131}I exposure. Participants were counted as cases for this outcome if they had colloid nodules, regardless of whether they had any other benign thyroid nodules. As shown in Table IX.D-8 below, 201(5.8%) of the 3440 living evaluable participants had benign colloid nodules.

Table IX.D-8. Benign Colloid Nodules, by Sex

Benign Colloid Nodules	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	136	7.8	65	3.8	201	5.8
No	1611	92.2	1628	96.2	3239	94.2
Total	1747	100.0	1693	100.0	3440	100.0

D.1.b. Pathways to Diagnosis of Benign Thyroid Nodules and Thyroid Nodules Suspicious for Follicular Neoplasm

The diagnoses described above were based primarily on diagnostic testing done at the HTDS clinics as well as the participants' prior medical records. As was done for thyroid cancer, the diagnoses that resulted from the HTDS clinical examinations were characterized according to the method of detection (or "pathway to diagnosis"). As described in section V.F above, the HTDS employed a comprehensive diagnostic design in which participants received a thyroid ultrasound scan that was viewed only after two independent thyroid physical examinations were conducted by thyroid specialists. Additional thyroid examinations were then conducted only if the ultrasound showed abnormalities that were not detected by the physicians.

Table IX.D-9 shows the method of detection for diagnoses of benign thyroid nodules, or nodules suspicious for follicular neoplasm, that resulted from HTDS examinations.

Table IX.D-9. Pathways to Diagnosis of Benign Thyroid Nodules and Thyroid Nodules Suspicious for Follicular Neoplasm

	Benign Thyroid Nodule		Suspicious for Follicular Neoplasm		Total	
Pathway To Diagnosis	No.	%	No.	%	No.	%
Palpable prior to ultrasound	104	47.3	7	41.2	110*	46.6
Palpable only after ultrasound	67	30.5	7	41.2	74	31.4
Palpable only (not detected on ultrasound)	15	6.8	0	--	15	6.4
Nonpalpable (detected only on ultrasound)	28	12.7	2	11.8	30	12.7
Uncertain consensus on physician exam	0	--	1	5.9	1	0.4
Complex cases: FNA decision based on combination of ultrasound and palpation	6	2.7	0	--	6	2.5
Total	220	100	17	100	236	100

* Note that one participant with both a benign thyroid nodule and a nodule suspicious for follicular neoplasm, both of which were palpable prior to ultrasound, is only counted once in the Total column.

The results in Table IX.D-9 show that about half of these diagnoses (125 or 51%) could have been detected by palpation alone. However nearly a third of these diagnoses (74 or 31%) required ultrasound review before they were detected by palpation. For 30 (13%) of these diagnoses, ultrasound was the only method that led to the diagnosis; these cases were relatively large, nonpalpable nodules (>1.5 cm in 3 dimensions) that were biopsied because of their size. None of these cases showed thyroid cancer. The relative frequencies of the various pathways to diagnosis were about the same for nodules suspicious for follicular neoplasm as for diagnoses of benign thyroid nodules. As indicated previously for thyroid cancer, these descriptive results illustrate the contributions of multiple diagnostic methods in the evaluation process. They also underscore the fairly large differences that can occur in the prevalence of thyroid disease from one study to another depending on the diagnostic methods used.

D.2. Analysis of Benign Thyroid Nodule Risk

D.2.a. Primary Analysis

Two hundred forty-nine living evaluable participants had diagnoses of benign thyroid nodule(s) based on HTDS or prior histology or cytology. Fourteen of these cases were out-of-area participants, for whom the CIDER program could not calculate dose estimates. The number of cases and proportion with benign thyroid nodule(s) are shown by sex, dose category and basis for diagnosis in Table IX.D-10. The numbers and proportions of cases of additional disease outcomes related to benign thyroid nodule are shown in Table IX.D-11.

Table IX.D-10. Diagnoses of Benign Thyroid Nodule by Sex, Dose Category, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Prior Histologic or Cytologic Diagnosis		1st Alternative Definition: Cases Based on HTDS or Prior Histology, Cytology, or Clinical Diagnosis		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%	No.	%
Out of Area	125	10	8.0	12	9.6	13	10.4
< 10	182	20	11.0	24	13.2	25	13.7
10-49	320	31	9.7	34	10.6	34	10.6
50-99	313	27	8.6	31	9.9	31	9.9
100-149	220	19	8.6	21	9.5	23	10.5
150-199	126	17	13.5	18	14.3	19	15.1
200-299	139	15	10.8	17	12.2	19	13.7
300-399	144	12	8.3	16	11.1	16	11.1
400-999	171	19	11.1	20	11.7	20	11.7
1000+	7	0	--	0	--	0	--
Total	1747	170	9.7	193	11.0	200	11.4

B. Male

Thyroid Radiation Dose	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Prior Histologic or Cytologic Diagnosis		1st Alternative Definition: Cases Based on HTDS or Prior Histology, Cytology, or Clinical Diagnosis		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%	No.	%
Out of Area	124	4	3.2	4	3.2	4	3.2
< 10	186	7	3.8	8	4.3	8	4.3
10-49	314	19	6.1	19	6.1	19	6.1
50-99	310	14	4.5	23	7.4	24	7.7
100-149	171	7	4.1	9	5.3	9	5.3
150-199	109	6	5.5	6	5.5	6	5.5
200-299	148	13	8.8	14	9.5	14	9.5
300-399	160	5	3.1	6	3.8	6	3.8
400-999	154	3	1.9	4	2.6	6	3.9
1000+	17	1	5.9	1	5.9	1	5.9
Total	1693	79	4.7	94	5.6	97	5.7

Table IX.D-11. Additional Disease Outcomes Related to Benign Thyroid Nodule by Sex and Estimated Dose (cases based on primary definition of benign thyroid nodule, i.e., HTDS or prior histologic or cytologic diagnoses only)

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Benign Thyroid Nodule or Nodule Suspicious for Follicular Neoplasm		Benign Thyroid Nodule Excluding Non-neoplastic Disease		Solitary Benign Thyroid Nodule Detected without Ultrasound		Benign Thyroid Nodule Excluding Colloid Only Nodules		Colloid Nodules	
(mGy)	No.	No.	%	No.	%	No.	%	No.	%	No.	%
OOA	125	11	8.8	8	6.4	5	4.0	9	7.2	7	5.6
< 10	182	23	12.6	14	7.7	5	2.7	18	9.9	14	7.7
10-49	320	32	10.0	24	7.5	15	4.7	27	8.4	25	7.8
50-99	313	30	9.6	15	4.8	13	4.2	26	8.3	20	6.4
100-149	220	21	9.5	15	6.8	3	1.4	18	8.2	17	7.7
150-199	126	18	14.3	12	9.5	7	5.6	17	13.5	13	10.3
200-299	139	15	10.8	11	7.9	4	2.9	14	10.1	10	7.2
300-399	144	13	9.0	6	4.2	5	3.5	12	8.3	12	8.3
400-999	171	21	12.3	12	7.0	7	4.1	17	9.9	18	10.5
1000+	7	0	--	0	--	0	--	0	--	0	--
Total	1747	184	10.5	117	6.7	64	3.7	158	9.0	136	7.8

B. Male

Thyroid Radiation Dose	Living Evaluable Female	Benign Thyroid Nodule or Nodule Suspicious for follicular neoplasm		Benign Thyroid Nodule Excluding Non-neoplastic Disease		Solitary Benign Nodule Detected without Ultrasound		Benign Thyroid Nodule Excluding Colloid Only Nodules		Colloid Nodules	
(mGy)	No.	No.	%	No.	%	No.	%	No.	%	No.	%
OOA	124	4	3.2	2	1.6	1	0.8	4	3.2	4	3.2
< 10	186	7	3.8	5	2.7	2	1.1	7	3.8	6	3.2
10-49	314	19	6.1	14	4.5	6	1.9	16	5.1	17	5.4
50-99	310	15	4.8	9	2.9	4	1.3	13	4.2	13	4.2
100-149	171	7	4.1	5	2.9	3	1.8	7	4.1	6	3.5
150-199	109	7	6.4	5	4.6	0	--	6	5.5	3	2.8
200-299	148	13	8.8	10	6.8	4	2.7	12	8.1	9	6.1
300-399	160	5	3.1	5	3.1	2	1.3	5	3.1	4	2.5
400-999	154	3	1.9	2	1.3	2	1.3	3	1.9	2	1.3
1000+	17	1	5.9	1	5.9	0	--	0	--	1	5.9
Total	1693	81	4.8	58	3.4	24	1.4	73	4.3	65	3.8

OOA = out of area participant

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in row 1 of Table IX.D-12 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was slightly less than zero (–0.008 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.022 to 0.041 per Gy, providing no evidence that cumulative incidence increased with increasing dose (one-tailed p = 0.68). The corresponding estimated background rates for diagnosis of benign thyroid nodule were 0.100 with confidence interval (0.081, 0.119) for women and 0.049 with confidence interval (0.034, 0.064) for men. Very similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data (Table IX.D-12, rows 2 and 3).

Table IX.D-12. Summary of Dose-Response Results for Diagnoses of Benign Thyroid Nodule

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS or prior, histologic or cytologic diagnosis)	Linear	Primary	None	MLE	.100 ± .008 (.081, .119)	.049 ± .006 (.034, .064)	–.008 ± .015 (< –.022, .041)	0.68
2.	Primary definition	Linear	Primary	None	LSU	.100 ± .007 (.082, .117)	.049 ± .008 (.031, .067)	–.006 ± .021 (–.055, .043)	0.61
3.	Primary definition	Linear	Primary	None	LSG	.101 ± .008 (.083, .119)	.050 ± .008 (.031, .069)	–.013 ± .024 (–.069, .044)	0.70
4.	Alternative def. #1 (HTDS or prior, histologic, cytologic, or clinical diagnosis)	Linear	Primary	None	MLE	.114 ± .008 (.094, .134)	.060 ± .007 (.044, .075)	–.013 ± .016 (< –.026, .037)	0.77
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.117 ± .008 (.096, .137)	.061 ± .007 (.044, .077)	–.008 ± .018 (< –.027, .046)	0.67
6.	Benign thyroid nodule and nodules suspicious for follicular neoplasm	Linear	Primary	None	MLE	.108 ± .008 (.089, .128)	.050 ± .006 (.036, .065)	–.008 ± .015 (< –.022, .041)	0.69

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.D-12. Summary of Dose-Response Results for Diagnoses of Benign Thyroid Nodule (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
7.	Benign thyroid nodule excluding non-neoplastic disease	Linear	Primary	None	MLE	.068 ± .007 (.052, .084)	.036 ± .005 (.024, .049)	–.003 ± .013 (< –.016, .039)	0.60
8.	Solitary benign thyroid nodule detected without ultrasound	Linear	Primary	None	MLE	.037 ± .005 (.024, .050)	.015 ± .004 (.006, .025)	–.005 ± .014 (< –.006, .032)	0.63
9.	Benign thyroid nodule excluding colloid only nodules	Linear	Primary	None	MLE	.095 ± .009 (.075, .116)	.047 ± .006 (.031, .062)	–.019 ± .025 (NE, .026)	0.91
10.	Benign colloid nodules	Linear	Primary	None	MLE	.080 ± .007 (.062, .097)	.039 ± .005 (.026, .052)	–.002 ± .015 (< –.018, .044)	0.56
11.	Primary definition	LQ	Primary	None	LSU	.100 ± .008 (.080, .120)	.049 ± .008 (.029, .070)	Lin: –.009 ± .035 (–.096, .078) Quad: .003 ± .023 (–.055, .060)	Quad: 0.90

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.D-12. Summary of Dose-Response Results for Diagnoses of Benign Thyroid Nodule (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Logistic	Primary	None	MLE	.100 (.081, .123)	.048 (.036, .065)	–.092 ± .316 (–.849, .666)	0.62
13.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.103 ± .009 (.082, .124)	.051 ± .007 (.035, .067)	–.021 ± .026 (< –.058, >.045)	0.79
14.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.098 ± .009 (.075, .120)	.051 ± .008 (.032, .070)	.001 ± .045 (–.102, .113)	0.49
15.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.098 ± .008 (.078, .118)	.047 ± .006 (.032, .062)	–.004 ± .017 (<–.021, .047)	0.60
16.	Primary definition	Linear	Alt. #1	None	MLE	.100 ± .008 (.081, .119)	.049 ± .006 (.034, .064)	–.007 ± .015 (< –.022, .039)	0.68
17.	Primary definition	Linear	Alt. #2	None	MLE	.101 ± .008 (.083, .119)	.050 ± .006 (.036, .065)	–.013 ± .010 (–.026, .023)	0.86
18.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.098 ± .008 (.080, .116)	.047 ± .006 (.034, .061)	–.004 ± .016 (< –.021, .045)	0.60
19.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.098 ± .008 (.080, .116)	.047 ± .006 (.034, .061)	–.005 ± .016 (< –.021, .044)	0.62

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

D.2.b. Alternative Definitions for Diagnosis of Benign Thyroid Nodule

Two alternative definitions for cases of benign thyroid nodule were considered. The first alternative added the 38 participants with HTDS or prior clinical diagnoses of benign thyroid nodule(s), for a total of 287 cases (271 in-area, and 16 out-of-area). The second added another 10 participants based solely on a report from the participant or his/her CATI respondent, for a total of 297 cases (280 in-area, and 17 out-of-area). As shown in rows 4 and 5 of Table IX.D-12 above, the parameter estimates for the linear dose-response model using either of these alternative definitions were essentially identical to those obtained in the primary analysis. In particular, the estimated slope of the linear dose-response model was less than zero for all three definitions of benign thyroid nodule, providing no evidence for any definition that the cumulative incidence of benign thyroid nodule increased with increasing dose ($p = 0.68$, 0.77, and 0.67 for the primary and first and second alternative definitions, respectively).

D.2.c. Additional Disease Outcomes Related to Benign Thyroid Nodule

D.2.c.1. Benign Thyroid Nodules and Nodules Suspicious for Follicular Neoplasm

Since most of the thyroid nodules classified as suspicious for follicular neoplasm were likely to be benign, the dose-response was also analyzed for the outcome of benign thyroid nodules and nodules suspicious for follicular neoplasm (Table IX.D-12, row 6). The estimated dose-response for this outcome was slightly negative (–0.008 per Gy with Bonferroni-adjusted 95% CI ranging from less than –0.022 to 0.041 per Gy), and consequently there was no evidence that the cumulative incidence of such nodules increased significantly with increasing dose ($p = 0.69$).

D.2.c.2 Benign Thyroid Nodule Excluding Non-neoplastic Disease

In order to investigate the possibility that a radiation-related increase in risk of benign thyroid nodules might be masked by the presence of nodules associated with other, nonradiogenic diseases, the dose-response was also analyzed for the outcome of benign thyroid nodule excluding non-neoplastic disease. The estimated dose-response for this outcome was also slightly negative (–0.003 per Gy with Bonferroni-adjusted 95% CI ranging from less than –0.016 to 0.039 per Gy, Table IX.D-12, row 7), and consequently there was no evidence that the cumulative incidence of such nodules increased significantly with increasing dose ($p = 0.60$).

D.2.c.3. Solitary Benign Thyroid Nodule Detected Without Ultrasound

As shown in row 8 of Table IX.D-12, the estimated slope of the dose-response for the outcome of solitary benign thyroid nodule detected without ultrasound was not significantly greater than zero (-0.005 per Gy, with Bonferroni-adjusted 95% confidence limits ranging from less than –0.006 to 0.032). Consequently there was no evidence that the cumulative incidence of such nodules increased significantly with increasing dose ($p = 0.63$).

D.2.c.4. Benign Thyroid Nodule Excluding Colloid-Only Nodules

The estimated slope of the dose-response for benign thyroid nodules excluding colloid-only nodules was slightly negative (–0.019 per Gy, Table IX.D-12, row 9). The Bonferroni-adjusted 95% lower confidence limit could not be estimated, and the upper confidence limit was 0.026 per Gy ($p = 0.91$).

D.2.c.5 Benign Colloid Nodules

The majority of participants with diagnoses of benign thyroid nodules had colloid nodules. Among the 3191 in-area participants, the cumulative incidence of colloid nodules did not increase significantly with increasing dose. As shown in row 10 of Table IX.D-12 above, the estimated slope was -0.002 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than -0.018 to 0.044 per Gy (p=0.56).

D.2.d. Alternative Dose-Response Functions

As shown in row 11 of Table IX.D-12, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.003 with Bonferroni-adjusted 95% confidence interval ranging from –0.055 to 0.060. Thus the addition of a quadratic term did not significantly improve the fit of the model (p = 0.90).

Parameter estimates for the sex-stratified logistic dose-response model [2] are shown in row 12 of Table IX.D-12. The estimated coefficient of radiation dose was less than zero (–0.092 per Gy, with Bonferroni-adjusted 95% confidence limits –0.849 and 0.666), providing no evidence that risk of benign thyroid nodule increased significantly with increasing dose (p = 0.62).

D.2.e. Effect of Excluding Participants in High Dose Categories

As rows 13 and 14 of Table IX.D-12 show, when participants in high dose categories were excluded, there was no evidence that the cumulative incidence of benign thyroid nodules increased with increasing dose.

D.2.f. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When participants in the Okanogan and Ferry/Stevens geostrata were excluded, the estimated slope B was not significantly greater than zero (-.004 per Gy, with Bonferroni-adjusted 95% CI ranging from less than -0.021 to 0.047 per Gy; Table IX.D-12, row 15), providing no evidence that the cumulative incidence of benign thyroid nodule increased with increasing dose (p=0.60).

D.2.g. Analysis of Benign Thyroid Nodules in Relation to Alternative Dose Estimates

As shown in rows 16 and 17 of Table IX.D-12, the cumulative incidence of benign thyroid nodule did not increase significantly in relation to either of the alternative dose estimates.

D.2.h. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 18 and 19 of Table IX.D-12, in both analyses the inclusion of the out-of-area participants had almost no effect on the estimated slope of the dose-response. In particular, the estimated slope of the dose-response was slightly negative in both scoping analyses, providing no evidence that cumulative incidence increased with increasing dose (p = 0.60 and 0.62 for the first and second scoping analysis, respectively).

D.2.i. Analysis of Benign Thyroid Nodule in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

D.2.i.1. Analysis by Geostratum

As shown in Table IX.D-13, among the entire 3440 living evaluable participants, the proportions with benign thyroid nodules ranged from 10/75 (13.3% in the Okanogan County geostratum) to 11/179 (6.1%, Richland) for women, and from 14/156 (9.0%, Adams County) to 2/76 (2.6%, Franklin County) for men ($p = 0.028$ for heterogeneity among the nine geostrata). In particular the percentages with benign thyroid nodules were somewhat higher in the Okanogan and Ferry/Stevens geostrata (11.9% for women, 6.0% for men) than in the remaining geostrata (9.5% and 4.6%, respectively; $p = 0.048$). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.D-13. Diagnoses of Benign Thyroid Nodule Based on HTDS or Prior Histologic or Cytologic Evidence, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	11	6.1	173	7	4.0	352	18	5.1
Pasco/Kennewick	508	42	8.3	501	13	2.6	1009	55	5.5
Benton County	376	43	11.4	358	23	6.4	734	66	9.0
Franklin County	73	7	9.6	76	2	2.6	149	9	6.0
Adams County	165	18	10.9	156	14	9.0	321	32	10.0
Walla Walla (city)	133	13	9.8	131	5	3.8	264	18	6.8
Walla Walla County	170	19	11.2	164	7	4.3	334	26	7.8
Okanogan County	75	10	13.3	64	4	6.3	139	14	10.1
Ferry/Stevens Counties	68	7	10.3	70	4	5.7	138	11	8.0
Total	1747	170	9.7	1693	79	4.7	3440	249	7.2

D.2.i.2. Analysis by Dichotomous Exposure Variable

Of the 1257 participants included in these analyses, 102 (8.1%) had a diagnosis of benign thyroid nodule(s) based on an HTDS or prior histologic or cytologic examination (see Table IX.D-14). These included 53/580 (9.1%) in the high exposure group and 49/677 (7.2%) in the low exposure group. After adjusting for the effects of sex and age at HTDS clinic in the logistic regression analysis, there was no statistically significant evidence that the cumulative incidence of benign thyroid nodule was elevated in the high exposure group ($p = 0.20$).

Table IX.D-14. Diagnoses of Benign Thyroid Nodule based on HTDS or Prior Histologic or Cytologic Evidence, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	34	9.7	326	15	4.6	677	49	7.2
High	298	36	12.1	282	17	6.0	580	53	9.1
Total	649	70	10.8	608	32	5.3	1257	102	8.1

D.2.j. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that confounding might influence the primary dose-response results, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of benign thyroid nodules, i.e., those with an HTDS or prior histologic or cytologic diagnosis, and on the primary dose estimates. Table IX.D-15 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, and < 180 days), age at HTDS examination, estimated dose from the NTS, history of any other cancer other than thyroid, and HTDS interview type (CATI versus expanded In-Person Interview).

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. Adjusting for the possibility of confounding by any of the other covariates in Table IX.D-15 did not markedly change the estimated regression coefficient. For example, adjusting for a potential confounding effect of exposure to Hanford's ^{131}I in the HEDR domain before age 180 days changed the estimated coefficient from –0.092 to –0.121, a small change when considered in relation to the confidence intervals for these two estimates, (–0.849, 0.666) and (–0.966, 0.724), respectively. Moreover the adjusted estimate remained less than zero. Consequently, there was no evidence that a confounding effect of this age covariate obscured a positive dose-response for benign thyroid nodule. This pattern is evident for all of the covariates other than sex in Table IX.D-15.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.D-15, the regression coefficients did not differ significantly between the groups defined by any of the covariates, suggesting that none of them was a significant modifier of a radiation dose-response for benign thyroid nodule.

Table IX.D-15. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid and Interview Type: Benign Thyroid Nodule

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	−.092 ± .316 (−.849, .666)	Not Applicable	−.454 ± .601 (−1.96, 1.05)	.070 ± .368 (−.849, .990)	.45
Prenatal exposure?	1034 / 3191	−.092 ± .316 (−.849, .666)	−.165 ± .324 (−1.00, .670)	−.147 ± .367 (−1.11, .821)	−.230 ± .687 (−2.04, 1.58)	.91
1st exposure before age 180 days?	1478 / 3191	−.092 ± .316 (−.849, .666)	−.113 ± .327 (−.954, .728)	−.161 ± .522 (−1.54, 1.22)	−.082 ± .414 (−1.18, 1.01)	.91
Age at exam >50?	2001 / 3191	−.092 ± .316 (−.849, .666)	−.222 ± .333 (−1.08, .634)	−.516 ± .737 (−2.46, 1.43)	−.135 ± .374 (−1.12, .853)	.64
NTS ^{131}I dose > 5.3 mGy?	1566 / 3187	−.097 ± .318 (−.858, .665)	−.109 ± .326 (−.949, .731)	.153 ± .393 (−.884, 1.19)	−.588 ± .608 (−2.19, 1.02)	.29
History of any cancer other than thyroid?	248 / 3186	−.091 ± .316 (−.848, .666)	−.091 ± .317 (−.909, .726)	−.263 ± .365 (−1.23, .700)	−.483 ± .560 (−.994, 1.96)	.30
Expanded In-Person Interview?	1212 / 3191	−.092 ± .316 (−.849, .666)	−.007 ± .319 (−.828, .814)	−.135 ± .497 (−1.45, 1.18)	−.083 ± .403 (−.980, 1.15)	.73

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.D-16 and IX.D-17 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Moreover the adjusted estimates all remained less than zero. Thus there was no evidence that a confounding effect of any of these covariates obscured a positive dose-response for benign thyroid nodule.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.D-16 and IX.D-17, with two possible exceptions.

- The estimated dose-response coefficient was markedly negative (−2.44) for the 398 participants with histories of IVP, but not for the majority of participants without such histories (0.118 with confidence interval ranging from −0.704 to 0.941; p=0.036).

- The estimated dose-response coefficient was markedly negative (−3.13) for the 442 participants with histories of occupations that might have involved exposure to radioactive materials or x-rays, but not for the majority of participants without such histories (0.112 with confidence interval ranging from −0.738 to 0.963; p=0.023).

The statistical significance of these differences must be interpreted with caution due to the large number of such comparisons that were performed. Moreover, neither of these two covariates identified a group of participants with a significantly positive dose-response.

Table IX.D-16. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Benign Thyroid Nodule

		Estimated Dose-Response Coefficient (per Gy)				
Ever Had: (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
CAT scan of the upper body?	775 / 3149	−.120 ± .320 (−.885, .646)	−.119 ± .319 (−.940, .701)	.057 ± .325 (−.800, .913)	−1.17± .88 (−3.51, 1.16)	.18
Diagnostic x-rays of the head?	1191 / 3155	−.063 ± .315 (−.816, .691)	−.057 ± .314 (−.866, .751)	.188 ± .353 (−.743, 1.12)	−.650 ± .626 (−2.30, 1.00)	.23
Diagnostic x-rays of the neck?	966 / 3167	−.085 ± .316 (−.842, .672)	−.109 ± .316 (−.924, .706)	−.051 ± .428 (−1.18, 1.08)	−.178 ± .477 (−1.44, 1.08)	.84
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	−.095 ± .317 (−.854, .664)	−.087 ± .317 (−.904, .730)	−.014 ± 1.23 (−3.27, 3.24)	−.092 ± .328 (−.959, .774)	.95
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	−.118 ± .325 (−.896, .659)	−.123 ± .325 (−.960, .715)	−.260 ± .379 (−1.26, .739)	.348 ± .629 (−1.31, 2.01)	.43
Barium enema?	825 / 3159	−.098 ± .317 (−.856, .660)	−.097 ± .317 (−.912, .719)	−.196 ± .382 (−1.20, .812)	.149 ± .562 (−1.33, 1.63)	.62
Upper GI?	1146 / 3177	−.117 ± .320 (−.882, .648)	−.116 ± .320 (−.940, .708)	−.154 ± .364 (−.806, 1.11)	−.696 ± .607 (−2.30, .906)	.22
Intravenous pyelogram?	398 / 3157	−.095 ± .318 (−.856, .667)	−.084 ± .319 (−.904, .737)	.118 ± .312 (−.704, .941)	−2.44 ± 1.33 (−5.96, 1.07)	.036
Fluoroscopy of the upper body?	246 / 3161	−.071 ± .316 (−.828, .686)	−.074 ± .317 (−.890, .742)	.022 ± .318 (−.818, .862)	−1.48 ± 1.42 (−5.21, 2.26)	.26
Nuclear scan (excluding thyroid scan)?	217 / 3162	−.091 ± .317 (−.851, .668)	−.088 ± .317 (−.905, .729)	−.017 ± .319 (−.859, .824)	−1.46 ± 1.61 (−5.71, 2.79)	.34
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	−.092 ± .316 (−.849, .666)	−.095 ± .317 (−.911, .720)	.143 ± .414 (−.949, 1.24)	−.380 ± .495 (−1.69, .927)	.41

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.D-17. Confounding and Effect Modification by Occupational History: Benign Thyroid Nodule

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
				Including Effect Modification		
		Unadjusted	Adjusted for Confounding	Group 0	Group 1	P
Any metal industry?	238 / 3191	−.092 ± .316 (−.849, .666)	−.083 ± .316 (−.896, .730)	−.090 ± .321 (−.937, .757)	.144 ± 1.77 (−4.53, 4.82)	.90
Any nuclear facility?	371 / 3191	−.092 ± .316 (−.849, .666)	−.094 ± .320 (−.917, .729)	−.127 ± .351 (−1.05, .798)	.081 ± .783 (−1.98, 2.15)	.81
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	−.092 ± .316 (−.849, .666)	−.114 ± .319 (−.936, .708)	.112 ± .322 (−.738, .963)	−3.13 ± 1.69 (−7.59, 1.33)	.023
Any of the above industries or occupations?	892 / 3191	−.092 ± .316 (−.849, .666)	−.062 ± .316 (−.875, .751)	−.045 ± .366 (−1.01, .922)	−.108 ± .623 (−1.75, 1.54)	.93

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.D-18 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.D-18. Confounding and Effect Modification by Smoking: Benign Thyroid Nodule

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
				Including Effect Modification		
		Unadjusted	Adjusted for Confounding	Group 0	Group 1	P
Cigarettes (unfiltered or filtered)?	1854 / 3183	−.087 ± .316 (−.843, .668)	−.085 ± .316 (−.899, .729)	−.135 ± .533 (−1.54, 1.27)	−.057 ± .390 (−1.09, .972)	.91
Any of cigarettes, cigar or pipe?	1900 / 3183	−.087 ± .316 (−.843, .668)	−.085 ± .316 (−.898, .729)	−.034 ± .535 (−1.45, 1.38)	−.111 ± .394 (−1.15, .927)	.91

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

D.2.k. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for benign thyroid nodule are shown in Figure IX.D-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates.

While the point estimate of the slope is greater than 0 for 30 of the 100 realizations, the confidence interval includes 0 for all 100 realizations. Also shown in Figure IX.D-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for the majority of realizations the estimated slope was less than 0.

Figure IX.D-1. Plot of Estimated Slope and 95% CI by Dose Realization: Benign Thyroid Nodule

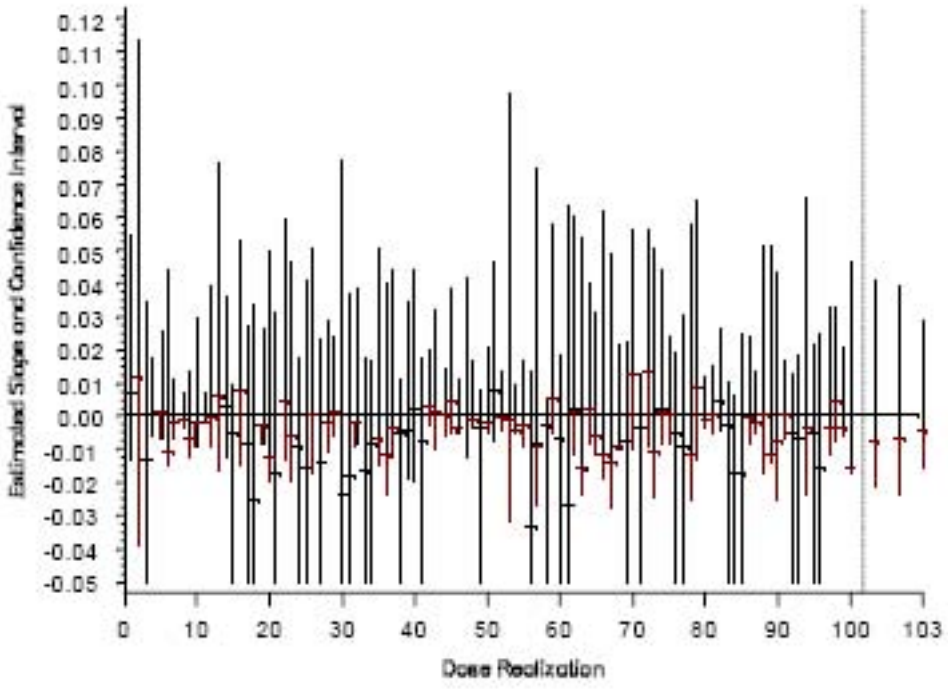
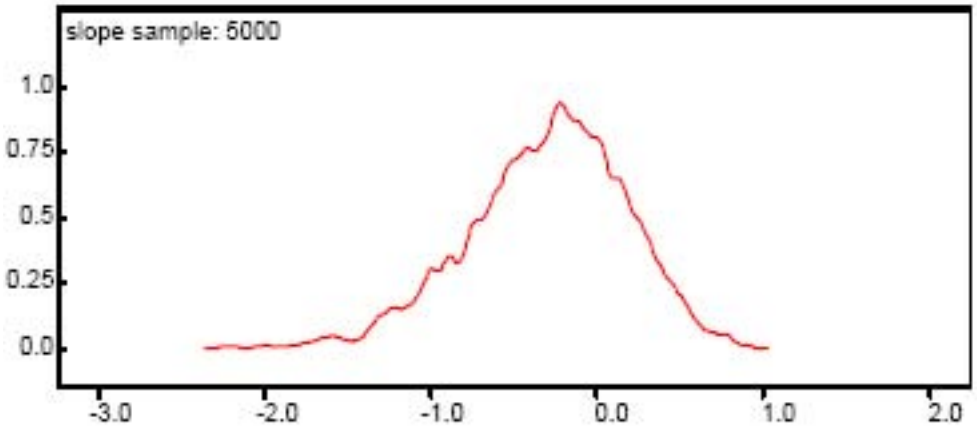


Figure IX.D-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –2.0 and 1.0. The estimate was less than or equal to 0 for 3608 of the 5000 replications, implying an empirical one-tailed p-value of 0.72. The median estimate was –0.25, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –1.60 and 0.70. These may be compared to the estimate of –.092 with confidence interval (–.849, .666) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of benign thyroid nodule increased with increasing dose.

Figure IX.D-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Benign Thyroid Nodule



E. Total Thyroid Neoplasia

E.1. Occurrence of Total Thyroid Neoplasia

The outcome of total thyroid neoplasia was defined to include participants with thyroid carcinoma based on HTDS or prior histology or benign thyroid nodule with a histologic type of follicular adenoma, based on HTDS or prior histology.

Among the 3440 living evaluable participants 33 (1.0%) had a diagnosis of total thyroid neoplasia, with the percentage of cases slightly higher for women (1.1%) compared to men (0.8%) (Table IX.E-1).

Table IX.E-1. Total Thyroid Neoplasia, by Sex

Diagnosis of Thyroid Cancer or Follicular Adenoma	Female		Male		Total	
	No.	%	No.	%	No.	%
Yes	20	1.1	13	0.8	33	1.0
No	1727	98.9	1680	99.2	3407	99.0
Total	1747	100.0	1693	100.0	3440	100.0

E.2. Analysis of Total Thyroid Neoplasia Risk

E.2.a. Primary Analysis

The proportions of living evaluable participants with total thyroid neoplasia are shown by sex, in-area status, and dose group in Table IX.E-2.

Table IX.E-2. Diagnoses of Total Thyroid Neoplasia by Sex and Dose Category

Thyroid Radiation Dose (mGy)	Female			Male		
	Living Evaluable	Primary Definition: Cases Based on HTDS or Prior Histologic Diagnosis		Living Evaluable	Primary Definition: Cases Based on HTDS or Prior Histologic Diagnosis	
	No.	No.	%	No.	No.	%
Out of Area	125	2	1.6	124	3	2.4
< 10	182	2	1.1	186	2	1.1
10-49	320	4	1.3	314	3	1.0
50-99	313	4	1.3	310	0	--
100-149	220	2	0.9	171	0	--
150-199	126	2	1.6	109	2	1.8
200-299	139	2	1.4	148	1	0.7
300-399	144	1	0.7	160	1	0.6
400-999	171	1	0.6	154	0	--
1000+	7	0	--	17	1	5.9
Total	1747	20	1.1	1693	13	0.8

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in row 1 of Table IX.E-3 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, the estimated slope B was 0.001 per Gy with Bonferroni-adjusted 95% CI ranging from less than –0.003 to 0.022 per Gy, providing no evidence that cumulative incidence increased with increasing dose (one-tailed p = 0.42). The corresponding estimated background rates for diagnosis of total thyroid neoplasia were 0.011 with confidence interval (0.004, 0.018) for women and 0.006 with confidence interval (0.001, 0.012) for men. Very similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data (Table IX.E-3, rows 2 and 3).

Table IX.E-3 Dose-Response Results for Diagnoses of Total Thyroid Neoplasia

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS or prior, histologic diagnosis)	Linear	Primary	None	MLE	.011 ± .003 (.004, .018)	.006 ± .002 (.001, .012)	.001 ± .006 (< –.003, .022)	0.42
2.	Primary definition	Linear	Primary	None	LSU	.011 ± .003 (.005, .017)	006 ± .003 (0*, .013)	.000 ± .007 (–.017, .018)	0.48
3.	Primary definition	Linear	Primary	None	LSG	.012 ± .003 (.006, .019)	.007 ± .003 (.001, .014)	–.006 ± .009 (–.026, .015)	0.75
4.	Primary definition	LQ	Primary	None	LSU	.011 ± .003 (.004, .019)	.007 ± .003 (0*, .014)	Lin: –.003 ± .013 (–.034, .028) Quad: .003 ± .008 (–.018, .023)	Quad: 0.74

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.E-3 Dose-Response Results for Diagnoses of Total Thyroid Neoplasia (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
5.	Primary definition	Logistic	Primary	None	MLE	.011 (.006, .021)	.006 (.003, .014)	.050 ± .833 (–1.94, 2.04)	0.48
6.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.012 ± .003 (.005, .020)	.007 ± .002 (.001, .012)	-.006 ± .007 (< –.007, >.017)	0.77
7.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.012 ± .003 (.004, .020)	.007 ± .003 (0*, .013)	-.001 ± .015 (–.034, .040)	0.53
8.	Primary definition	Linear	Primary	Exclude OK and F/S geostrata	MLE	.010 ± .003 (.003, .016)	.006 ± .002 (.000, .012)	.002 ± .007 (<–.003, .023)	0.37

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.E-3 Dose-Response Results for Diagnoses of Total Thyroid Neoplasia (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
9.	Primary definition	Linear	Alt. #1	None	MLE	.012 ± .003 (.004, .019)	007 ± .003 (.000, .013)	-.003 ± .009 (NE, .015)	0.77
10.	Primary definition	Linear	Alt. #2	None	MLE	.011 ± .003 (.004, .018)	007 ± .003 (.001, .013)	-.003 ± .010 (NE, .010)	0.85
11.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.012 ± .003 (.005, .018)	.008 ± .002 (.002, .014)	-.001 ± .006 (<-.003, .019)	0.55
12.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.012 ± .003 (.005, .018	.008 ± .002 (.002, .014)	-.001 ± .006 (<-.003, >.018)	0.58

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, OK = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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E.2.b. Alternative Dose-Response Functions

As shown in row 4 of Table IX.E-3, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.003 with Bonferroni-adjusted 95% confidence interval ranging from –0.018 to 0.023. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.74$).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.050 with Bonferroni-adjusted 95% CI ranging from –1.94 to 2.04 (Table IX.E-3, row 5). Thus there was no evidence from the logistic regression model that cumulative incidence of total thyroid neoplasia increased significantly with increasing dose ($p = 0.48$).

E.2.c. Effect of Excluding Participants in High Dose Categories

As shown in rows 6 and 7 of Table IX.E-3, excluding participants with doses above 1000 mGy or above 400 mGy resulted in slightly negative estimates for the slope of the dose-response, thus providing no evidence that risk increased with increasing dose ($p = 0.77$ and 0.53 based on participants with doses $\leq$ 1000 mGy and $\leq$ 400 mGy, respectively).

E.2.d. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

As shown in row 8 of Table IX.E-3, if participants from the Okanogan and Ferry/Stevens geostrata are excluded, the estimated slope of the dose-response is 0.002 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than - 0.003 to 0.023 per Gy; $p = 0.37$).

E.2.e. Analysis of Total Thyroid Neoplasia in Relation to Alternative Dose Estimates

As shown in rows 9 and 10 of Table IX.E-3, the cumulative incidence of total thyroid neoplasia did not increase significantly in relation to either of the alternative dose estimates.

E.2.f. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 11 and 12 of Table IX.E-3, in both analyses the inclusion of the out-of-area participants slightly decreased the estimated slope of the dose-response, but did not materially change the dose-response results.

E.2.g. Analysis of Total Thyroid Neoplasia in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

E.2.g.1. Analysis by Geostratum

As shown in Table IX.E-4, among the entire 3440 living evaluable participants, the proportions with thyroid neoplasia ranged from 0/73 (0% in the Franklin County geostratum) to 2/68 (2.9%, Ferry/Stevens Counties) for women, and from 0/76 (0%, Franklin County) to 1/64 (1.6%, Okanogan County) for men ($p = 0.41$ for heterogeneity among the nine geostrata). In particular the percentages with thyroid neoplasia were somewhat higher in the Okanogan and Ferry/Stevens geostrata (2.8% for women, 1.5% for men) than in the remaining geostrata (1.0% and 0.7%, respectively; $p = 0.037$). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.E-4. Diagnoses of Total Thyroid Neoplasia Based On Histologic or Cytologic Evidence from or Prior to the HTDS, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	2	1.1	173	1	0.6	352	3	0.9
Pasco/Kennewick	508	4	0.8	501	3	0.6	1009	7	0.7
Benton County	376	5	1.3	358	4	1.1	734	9	1.2
Franklin County	73	0	--	76	0	--	149	0	--
Adams County	165	2	1.2	156	1	0.6	321	3	0.9
Walla Walla (city)	133	1	0.8	131	1	0.8	264	2	0.8
Walla Walla County	170	2	1.2	164	1	0.6	334	3	0.9
Okanogan County	75	2	2.7	64	1	1.6	139	3	2.2
Ferry/Stevens Counties	68	2	2.9	70	1	1.4	138	3	2.2
Total	1747	20	1.1	1693	13	0.8	3440	33	1.0

E.2.g.2. Analysis by Dichotomous Exposure Variable

Of the 1257 participants included in these analyses, 16 (1.3%) had a diagnosis of total thyroid neoplasia based on an HTDS or prior histologic or cytologic examination (see Table IX.E-5). These included 5/580 (0.9%) in the high exposure group and 11/677 (1.6%) in the low exposure group. After adjusting for the effects of sex and age at HTDS clinic in the logistic regression analysis, there was no statistically significant evidence that the cumulative incidence of total thyroid neoplasia was elevated in the high exposure group ($p = 0.73$).

Table IX.E-5. Diagnoses of Total Thyroid Neoplasia Based on HTDS or Prior Histologic or Cytologic Evidence, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	6	1.7	326	5	1.5	677	11	1.6
High	298	3	1.0	282	2	0.7	580	5	0.9
Total	649	9	1.4	608	7	1.2	1257	16	1.3

E.2.h. Confounding and Effect Modification

There were too few participants with diagnoses in the category of total thyroid neoplasia to warrant any analysis of confounding or effect modification.

E.2.i. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for total thyroid neoplasia are shown in Figure IX.E-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 47 of the 100 realizations, the confidence interval includes 0 for all 100 realizations. Also shown in Figure IX.E-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations dose. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for about half of the realizations the estimated slope was less than 0.

Figure IX.E.1 Plot of Estimated Slope and 95% CI by Dose Realization: Total Thyroid Neoplasia

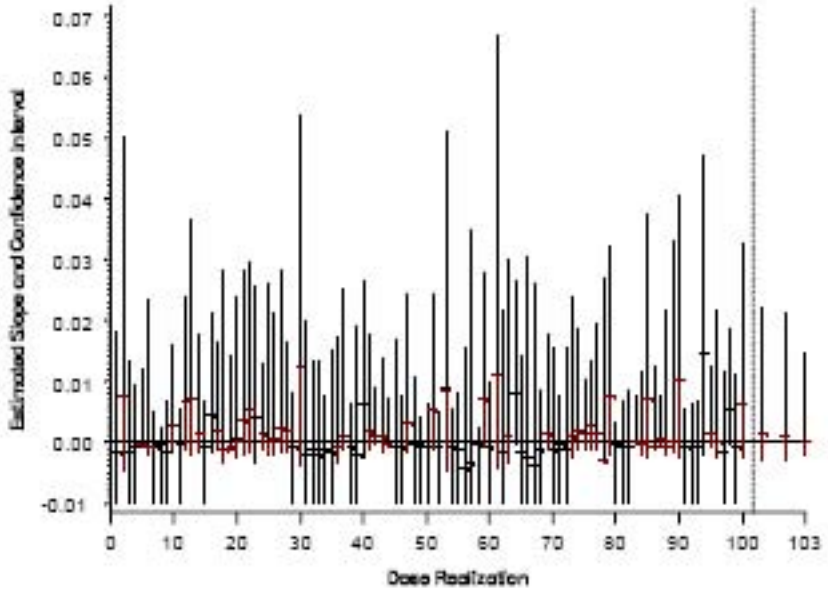
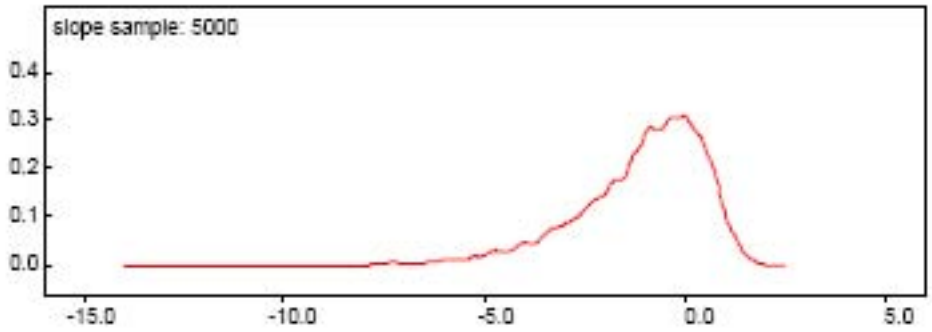


Figure IX.E-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –6.0 and 1.5. The estimate was less than or equal to 0 for 3640 of the 5000 replications, implying an empirical one-tailed p-value of 0.73. The median estimate was –0.73, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –6.78 and 1.42. These may be compared to the estimate of 0.050 with confidence interval (–1.94, 2.04) obtained using the median dose estimates without adjustment for uncertainty. Thus this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of thyroid neoplasia increased with increasing dose.

Figure IX.E-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Total Thyroid Neoplasia



F. Any Thyroid Nodule

F.1. Occurrence of Any Thyroid Nodule

The primary and alternative definitions for the outcome of any thyroid nodule were as follows:

- Primary definition: HTDS or prior, histologic or cytologic diagnosis (281 cases)
- Alternative definition #1: HTDS or prior, histologic, cytologic or clinical diagnosis (320 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (330 cases).

The outcome of any thyroid nodule was defined by the presence of a diagnosis of one or more of benign thyroid nodule, thyroid carcinoma, or nodule suspicious for follicular neoplasm. Table IX.F-1 shows that 281 (8.2%) living evaluable participants had a diagnosis of any thyroid nodule based on histologic or cytologic evidence from the HTDS or prior, with the percentage about twice as high for women (11.0%) as for men (5.2%). Another 1.1% was based on clinical diagnoses by the HTDS or prior. There were 10 living evaluable participants with a diagnosis of any thyroid nodule based on reports from the participant or his/her CATI respondent.

Table IX.F-1. Basis for Diagnosis of Any Thyroid Nodule Disease, by Sex

	Female		Male		Total	
Diagnosis of Any Thyroid Nodule	No.	%	No.	%	No.	%
Yes	224	12.8	106	6.3	330	9.6
• Histologic diagnosis: HTDS	11	0.6	12	0.7	23	0.7
• Cytologic diagnosis: HTDS	156	8.9	67	4.0	223	6.5
• Prior histologic diagnosis	24	1.4	8	0.5	32	0.9
• Prior cytologic diagnosis	2	0.1	1	0.1	3	0.1
• Clinical diagnosis: HTDS	16	0.9	13	0.8	29	0.8
• Clinical diagnosis: prior	8	0.5	2	0.1	10	0.3
• Participant/respondent report	7	0.4	3	0.2	10	0.3
No	1521	87.1	1586	93.7	3107	90.3
Unknown	2	0.1	1	0.1	3	0.1
Total	1747	100.0	1693	100.0	3440	100.0

F.1.a. Additional Disease Outcomes Related to Any Thyroid Nodule

F.1.a.1. Any Solitary Thyroid Nodule Detected without Ultrasound

The outcome of any palpable solitary thyroid nodule detected without ultrasound was defined in order to simulate the effect of screening for thyroid disease by palpation only, i.e., without ultrasound examination. This analysis allows us to compare the prevalence of thyroid nodularity with older studies (e.g. The Framingham Study) that used only palpation to determine the prevalence of nodular thyroid disease. In HTDS a total of 117 living evaluable participants (83 women, 34 men) had diagnoses of such nodules (Table IX.F-2).

Table IX.F-2. Any Solitary Thyroid Nodule Detected without Ultrasound, by Sex

Any Solitary Thyroid Nodule	Female		Male		Total	
Detected without Ultrasound	No.	%	No.	%	No.	%
Yes	83	4.8	34	2.0	117	3.4
No	1664	95.2	1659	98.0	3323	96.6
Total	1747	100.0	1693	100.0	3440	100.0

For the majority of the 117 living evaluable participants with solitary thyroid nodules that were detected without ultrasound, i.e., by palpation, those nodules were also observed on the ultrasound examination. However for 21 (18%) of the 117, those nodules were not detected by ultrasound. Twelve (57%) of these 21 participants each had 1-6 discrete focal ultrasound abnormalities in addition to the palpable nodule which was not detected on ultrasound. In addition, 15 of 21 (71%) had documented Hashimoto's thyroiditis. Only 4 participants (0.1% of the 3429 living evaluable participants whose thyroid glands were visible in their ultrasound examinations) had a palpable nodule with a completely normal ultrasound scan. These results suggest that the reason for the discordance between palpation and ultrasound in this small group was the abnormal thyroid tissue that is present throughout the gland in individuals with Hashimoto's thyroiditis, a fact well known in clinical practice. Since only 4 participants had true palpable nodules that were not detected by ultrasound, a dose-response analysis of this specific outcome was not feasible.

F.2. Analysis of Any Thyroid Nodule Risk

F.2.a. Primary Analysis

The proportions with any thyroid nodule are shown by sex, in-area status, and dose group in Table IX.F-3 below. The numbers and proportions with diagnoses of any solitary thyroid nodule detected without ultrasound are also shown.

Table IX.F-3. Diagnoses of Any Thyroid Nodule by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Prior Histologic or Cytologic Diagnosis		1st Alternative Definition:Cases Based on HTDS or Prior Histology, Cytology, or Clinical Diagnosis		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report		Any Solitary Thyroid Nodule Detected without Ultrasound	
	No.	No.	%	No.	No.	%	%	No.	%
OOA	125	13	10.4	16	12.8	17	13.6	7	5.6
< 10	182	24	13.2	28	15.4	29	15.9	8	4.4
10-49	320	34	10.6	37	11.6	37	11.6	18	5.6
50-99	313	31	9.9	35	11.2	35	11.2	16	5.1
100-149	220	22	10.0	24	10.9	26	11.8	5	2.3
150-199	126	19	15.1	20	15.9	21	16.7	8	6.3
200-299	139	15	10.8	17	12.2	19	13.7	4	2.9
300-399	144	14	9.7	18	12.5	18	12.5	7	4.9
400-999	171	21	12.3	22	12.9	22	12.9	10	5.8
1000+	7	0	--	0	--	0	--	0	--
Total	1747	193	11.0	217	12.4	224	12.8	83	4.8

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Prior Histologic or Cytologic Diagnosis		1st Alternative Definition:Cases Based on HTDS or Prior Histology, Cytology, or Clinical Diagnosis		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report		Any Solitary Thyroid Nodule Detected without Ultrasound	
	No.	No.	%	No.	No.	%	%	No.	%
OOA	124	7	5.6	7	5.6	7	5.6	3	2.4
< 10	186	8	4.3	9	4.8	9	4.8	3	1.6
10-49	314	21	6.7	21	6.7	21	6.7	7	2.2
50-99	310	15	4.8	24	7.7	25	8.1	6	1.9
100-149	171	7	4.1	9	5.3	9	5.3	3	1.8
150-199	109	7	6.4	7	6.4	7	6.4	1	0.9
200-299	148	13	8.8	14	9.5	14	9.5	6	4.1
300-399	160	5	3.1	6	3.8	6	3.8	2	1.3
400-999	154	3	1.9	4	2.6	6	3.9	3	1.9
1000+	17	2	11.8	2	11.8	2	11.8	0	--
Total	1693	88	5.2	103	6.1	106	6.3	34	2.0

OOA = out of area

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in row 1 of Table IX.F-4 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, the estimated slope B was slightly less than zero (–0.007 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.023 to 0.043 per Gy, providing no evidence that cumulative incidence increased with increasing dose (one-tailed p = 0.65). The corresponding estimated background rates for outcome of any thyroid nodule were 0.112 with confidence interval (0.092, 0.132) for women and 0.053 with confidence interval (0.038 to 0.068) for men. Very similar results were obtained when the model was fit by least squares using ungrouped or grouped data (Table IX.F-4, rows 2 and 3).

Table IX.F-4. Dose-Response Results for Diagnoses of Any Thyroid Nodule

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS or prior, histologic or cytologic diagnosis)	Linear	Primary	None	MLE	.112 ± .008 (.092, .132)	.053 ± .006 (.038, .068)	-.007 ± .016 (<-.023, .043)	0.65
2.	Primary definition	Linear	Primary	None	LSU	.112 ± .008 (.094, .131)	.053 ± .008 (.034, .072)	–.006 ± .022 (–.058, .045)	0.61
3.	Primary definition	Linear	Primary	None	LSG	.114 ± .008 (.095, .133)	.055 ± .008 (.035, .074)	–.017 ± .025 (–.078, .043)	0.75
4.	Alternative def. #1 (HTDS or prior, histologic, cytologic, or clinical diagnosis)	Linear	Primary	None	MLE	.126 ± .009 (.105, .147)	.063 ± .007 (.047, .080)	-.012 ± .017 (<-.028, .039)	0.75
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.129 ± .009 (.108, .150)	.064 ± .007 (.048, .081)	-.007 ± .019 (<-.029, .047)	0.65

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value,"NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.F-4. Dose-Response Results for Diagnoses of Any Thyroid Nodule (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Solitary thyroid nodule detected without ultrasound	Linear	Primary	None	MLE	.047 ± .006 (.032, .061)	.020 ± .004 (.009, .030)	.001 ± .015 (<-.009, .042)	0.46
7.	Primary definition	LQ	Primary	None	LSU	.113 ± .008 (.092, .134)	.054 ± .009 (.032, .075)	Lin: –.014 ± .037 (–.105, .078) Quad: .006 ± .024 (–.054, .066)	Quad: 0.80
8.	Primary definition	Logistic	Primary	None	MLE	.112 (.092, .137)	.052 (.039, .070)	-.09 ± .30 (-.81, .63)	0.62
9.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.117 ± .009 (.095, .140)	.055 ± .007 (.039, .072)	-.032 ± .026 (<-.062, >.035	0.88
10.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.112 ± .010 (.089, .135)	.056 ± .008 (.037, .076)	-.017 ± .046 (-.122, .099)	0.64
11.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.108 ± .009 (.087, .129)	.051 ± .007 (.035, .067)	-.003 ± .018 (<-.023, .050)	0.56
12.	Primary definition	Linear	Alt. #1	None	MLE	.113 ± .008 (.093, .133)	.054 ± .006 (.038, .069)	-.010 ± .015 (<-.024, .036)	0.74

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value,"NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.F-4. Dose-Response Results for Diagnoses of Any Thyroid Nodule (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
13.	Primary definition	Linear	Alt. #2	None	MLE	.114 ± .008 (.094, .133)	.055 ± .006 (.040, .069)	-.015 ± .010 (-.028, .021)	0.88
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.111 ± .008 (.092, .131)	.053 ± .006 (.038, .067)	-.006 ± .016 (<-.023, .043)	0.64
15.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.112 ± .008 (.093, .131)	.053 ± .006 (.039, .068)	-.007 ± .016 (<-.023, >.041)	0.66

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value,"NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

F.2.b. Alternative Definitions for Diagnosis of Any Thyroid Nodule

Two alternative definitions for cases of any thyroid nodule were considered. The first alternative added the 39 participants with HTDS or prior clinical diagnoses of any thyroid nodule, for a total of 320 (297 in-area, 23 out-of-area) cases. The second alternative criterion for defining cases of nodular disease added another 10 participants based solely on a report from the participant or his/her CATI respondent, for a total of 330 (306 in-area, 24 out-of-area) cases. As shown in rows 4 and 5 of Table IX.F-4 above, there was no evidence that the cumulative incidence of any thyroid nodule increased with increasing dose for either of these alternative definitions.

F.2.c. Additional Disease Outcomes Related to Any Thyroid Nodule

F.2.c.1. Any Solitary Thyroid Nodule Detected Without Ultrasound

As shown in row 6 of Table IX.F-4, the estimated slope of the dose-response for the outcome of any solitary thyroid nodule detected without ultrasound was not significantly greater than zero (0.001 per Gy with Bonferroni-adjusted 95% CI ranging from less than –0.009 to 0.042 per Gy). Consequently there was no evidence that the cumulative incidence of such nodules increased significantly with increasing dose ($p = 0.46$).

F.2.d. Alternative Dose-Response Functions

As shown in row 7 of Table IX.F-4, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.006 with Bonferroni-adjusted 95% confidence interval ranging from –0.054 to 0.066. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.80$).

In the analysis of any thyroid nodule based on HTDS or prior histologic or cytologic evidence, i.e., the primary criterion for defining cases with any thyroid nodule, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –0.09 with Bonferroni-adjusted 95% confidence interval ranging from –0.81 to 0.63 (Table IX.F-4, row 8). Thus there was no evidence from the logistic regression model that cumulative incidence of any thyroid nodule increased with increasing dose ($p = 0.62$).

F.2.e. Effect of Excluding Participants in High Dose Categories

As shown in rows 9 and 10 of Table IX.F-4, when participants in high dose categories were excluded, there was no evidence that the cumulative incidence of any thyroid nodule increased with increasing dose.

F.2.f. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

Excluding Okanogan and Ferry/Stevens geostrata had no effect on the dose-response results, namely, there was no evidence that cumulative incidence of any thyroid nodule increased with increasing dose ($p = 0.56$; Table IX.F-4, row 11).

F.2.g. Analysis of Any Thyroid Nodule in Relation to Alternative Dose Estimates

When the first set of alternative dose estimates were used, the estimated slope B was -0.010 per Gy with Bonferroni-adjusted 95% confidence interval ranging from less than –0.024 to 0.036 (Table IX.F-4, row 12). For the second set of alternative dose estimates the estimated slope B was –0.015 per Gy with Bonferroni adjusted 95% confidence interval ranging from less than –0.028 to 0.021 (Table IX.F-4, row 13). Thus, for neither set of alternative dose estimates was there any evidence that the cumulative incidence of any thyroid nodule increased with increasing dose ($p = 0.74$ and 0.88 for the first and second set of alternative dose estimates, respectively).

F.2.h. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As shown in rows 14 and 15 of Table IX.F-4, for neither scoping analysis was there any evidence that the cumulative incidence of any thyroid nodule increased with increasing dose ($p = 0.64$ and 0.66 for the first and second scoping analyses, respectively).

F.2.i. Analysis of Any Thyroid Nodule in Relation to Alternative Representations of Exposure

In both the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

F.2.i.1. Analysis by Geostratum

As shown in Table IX.F-5, among the entire 3440 living evaluable participants, the proportions with any thyroid nodule (based on an HTDS or prior histologic or cytologic diagnosis) ranged from 12/75 (16.0% in the Okanogan County geostratum) to 14/179 (7.8%, Richland) for women, and from 14/156 (9.0%, Adams County) to 2/76 (2.6%, Franklin County) for men ($p = 0.032$ for heterogeneity among the nine geostrata). In particular the percentages with any thyroid nodule were somewhat higher in the Okanogan and Ferry/Stevens geostrata (15.4% for women, 6.7% for men) than in the remaining geostrata (10.7% and 5.1%, respectively; $p = 0.010$). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.F-5. Diagnoses of Any Thyroid Nodule with at Least One Outcome Based On Histologic or Cytologic Evidence from or Prior to the HTDS

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	14	7.8	173	8	4.6	352	22	6.3
Pasco/Kennewick	508	49	9.6	501	16	3.2	1009	65	6.4
Benton County	376	45	12.0	358	25	7.0	734	70	9.5
Franklin County	73	7	9.6	76	2	2.6	149	9	6.0
Adams County	165	20	12.1	156	14	9.0	321	34	10.6
Walla Walla (city)	133	15	11.3	131	6	4.6	264	21	8.0
Walla Walla County	170	21	12.4	164	8	4.9	334	29	8.7
Okanogan County	75	12	16.0	64	5	7.8	139	17	12.2
Ferry/Stevens Counties	68	10	14.7	70	4	5.7	138	14	10.1
Total	1747	193	11.0	1693	88	5.2	3440	281	8.2

F.2.i.2. Analysis by Dichotomous Exposure Variable

A total of 118 (9.4%) of the 1257 participants included in these analyses had a diagnosis of any thyroid nodule based on an HTDS or prior histologic or cytologic examination (see Table IX.F-6). These included 57/580 (9.8%) in the high exposure group and 61/677 (9.0%) in the low exposure group. After adjusting for the effects of sex and age at HTDS clinic in the logistic regression analysis, there was no evidence of greater cumulative incidence of any thyroid nodule in the high exposure group ($p = 0.38$).

Table IX.F-6. Diagnoses of Any Thyroid Nodule Based on HTDS or Prior Histologic or Cytologic Evidence, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	42	12.0	326	19	5.8	677	61	9.0
High	298	39	13.1	282	18	6.4	580	57	9.8
Total	649	81	12.5	608	37	6.1	1257	118	9.4

F.2.j. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of any thyroid nodule, i.e., those with an HTDS or prior histologic or cytologic diagnosis, and on the primary dose estimates. Table IX.F-7 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. It is evident from Table IX.F-7 that the model was not significantly improved by adjusting for any of the other factors as a potential confounder: none produced a significantly better fit to the data. Since the estimated slope was virtually unaffected by such adjustments, it does not appear that omitting these factors introduces any important bias in the dose-response results.

Table IX.F-7. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid and Interview Type: Any Thyroid Nodule

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	−.087 ± .301 (−.808, .634)	Not Applicable	−.311 ± .555 (−1.70, 1.08)	.016 ± .357 (−.875, .908)	.62
Prenatal exposure?	1034 / 3191	−.087 ± .301 (−.808, .634)	−.150 ± .308 (−.943, .643)	−.064 ± .340 (−.962, .834)	−.461 ± .685 (−2.26, 1.35)	.58
1st exposure before age 180 days?	1478 / 3191	−.087 ± .301 (−.808, .634)	−.103 ± .310 (−.901, .695)	−.292 ± .510 (−1.64, 1.05)	.008 ± .375 (−.983, .998)	.64
Age at exam > 50?	2001 / 3191	−.087 ± .301 (−.808, .634)	−.180 ± .313 (−.987, .627)	−.064 ± .570 (−1.57, 1.44)	−.227 ± .373 (−1.21, .757)	.81
NTS ^{131}I dose > 5.3 mGy?	1566 / 3187	−.092 ± .303 (−.816, .633)	−.084 ± .308 (−.878, .711)	.183 ± .375 (−.805, 1.17)	−.551 ± .567 (−2.05, .944)	.26
History of any cancer other than thyroid?	248 / 3186	−.087 ± .301 (−.807, .634)	−.083 ± .303 (−.863, .698)	−.234 ± .344 (−1.14, .673)	.483 ± .560 (−.994, 1.96)	.31
Expanded in-person interview?	1212 / 3191	−.087 ± .301 (−.808, .634)	.012 ± .303 (−.768, .793)	.050 ± .459 (−1.16, 1.26)	−.016 ± .408 (−1.09, 1.06)	.91

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.F-8 and IX.F-9 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Moreover the adjusted estimates all remained less than zero. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for the outcome of any thyroid nodule.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.F-8 and IX.F-9, with two possible exceptions.

- The estimated dose-response coefficient was markedly negative (–2.22) for the 398 participants with histories of intravenous pyelograms (IVPs), but not markedly different for the majority of participants without such histories (0.113 with confidence interval ranging from –0.675 to 0.900; p = 0.040).

- The estimated dose-response coefficient was markedly negative (–2.75) for the 442 participants with histories of occupations that might have involved exposure to radioactive materials or x-rays, but not markedly different for the majority of participants without such histories (0.103 with confidence interval ranging from –0.711 to 0.918; p= 0.031).

The statistical significance of these differences must be interpreted with caution due to the large number of such comparisons that were performed. Moreover, neither of these two covariates identified a group of participants with a significantly positive dose-response.

Table IX.F-8. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Any Thyroid Nodule

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
CAT scan of the upper body?	775 / 3149	−.115 ± .305 (−.844, .615)	−.110 ± .303 (−.890, .669)	.073 ± .306 (−.735, .881)	−1.32± .89 (−3.66, 1.02)	.12
Diagnostic x-rays of the head?	1191 / 3155	−.060 ± .300 (−.777, .658)	−.062 ± .299 (−.833, .709)	.131 ± .339 (−.763, 1.02)	−.554 ± .602 (−2.14, 1.03)	.31
Diagnostic x-rays of the neck?	966 / 3167	−.081 ± .301 (−.801, .640)	−.104 ± .302 (−.882, .675)	.111 ± .394 (−.928, 1.15)	−.393 ± .501 (−1.72,.930)	.42
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	−.090 ± .302 (−.813, .632)	−.077 ± .302 (−.854, .700)	−.215 ± 1.23 (−3.46, 3.03)	−.068 ± .311 (−.888, .752)	.91
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	−.109 ± .308 (−.848, .629)	−.111 ± .308 (−.906, .683)	−.138 ± .347 (−1.05, .778)	−.007 ± .675 (−1.79, 1.77)	.86
Barium enema?	825 / 3159	−.094 ± .301 (−.815, .628)	−.093 ± .302 (−.869, .684)	−.056 ± .348 (−.974, .862)	−.198 ± .604 (−1.79, 1.40)	.84
Upper GI?	1146 / 3177	−.110 ± .304 (−.838, .618)	−.113 ± .304 (−.897, .671)	.041 ± .364 (−.920, 1.00)	−.401 ± .535 (−1.81, 1.01)	.49
Intravenous pyelogram?	398 / 3157	−.090 ± .303 (−.814, .635)	−.078 ± .303 (−.859, .703)	.113 ± .299 (−.675, .900)	−2.22 ± 1.22 (−5.45, 1.01)	.040
Fluoroscopy of the upper body?	246 / 3161	−.057 ± .300 (−.776, .662)	−.061 ± .301 (−.836, .714)	.054 ± .300 (−.738, .847)	−1.90 ± 1.45 (−5.73, 1.92)	.14
Nuclear scan (excluding thyroid scan)?	217 / 3162	−.086 ± .302 (−.809, .636)	−.084 ± .302 (−.862, .694)	.021 ± .300 (−.771, .814)	−2.30 ± 1.71 (−6.80, 2.20)	.13
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	−.087 ± .301 (−.808, .634)	−.088 ± .301 (−.865, .688)	.344 ± .375 (−.645, 1.33)	−.662 ± .506 (−2.00, .674)	.103

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.F-9. Confounding and Effect Modification by Occupational History: Any Thyroid Nodule

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes/ Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Any metal industry?	238 / 3191	−.087 ± .301 (−.808, .634)	−.079 ± .300 (−.853, .695)	−.085 ± .305 (−.890, .720)	.144 ± 1.77 (−4.53, 4.82)	.90
Any nuclear facility?	371 / 3191	−.087 ± .301 (−.808, .634)	−.080 ± .303 (−.860, .701)	−.187 ± .341 (−1.09, .713)	.418 ± .661 (−1.33, 2.16)	.44
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	−.087 ± .301 (−.808, .634)	−.105 ± .304 (−.887, .677)	.103 ± .309 (−.711, .918)	−2.75 ± 1.53 (−6.80, 1.30)	.031
Any of the above industries or occupations?	892 / 3191	−.087 ± .301 (−.808, .634)	−.057 ± .301 (−.832, .717)	−.118 ± .358 (−1.06, .827)	−.097 ± .547 (−1.35, 1.54)	.74

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.F-10 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.F-10. Confounding and Effect Modification by Smoking: Any Thyroid Nodule

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Cigarettes (unfiltered or filtered)?	1854 / 3183	−.083 ± .301 (−.803, .637)	−.083 ± .301 (−.858, .691)	−.198 ± .520 (−1.57, 1.17)	−.024 ± .364 (−.984, .936)	.78
Any of cigarettes, cigar or pipe?	1900 / 3183	−.083 ± .301 (−.803, .637)	−.083 ± .301 (−.858, .691)	−.105 ± .523 (−1.48, 1.27)	−.072 ± .367 (−1.04, .895)	.96

Entries in the table are estimate ± standard error for the regression coefficient, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

F.2.k. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for any thyroid nodule are shown in Figure IX.F-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates.

While the point estimate of the slope is greater than 0 for 32 of the 100 realizations, the confidence interval includes 0 for all 100 of the realizations. Also shown in Figure IX.F-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for the majority of realizations the estimated slope was less than 0.

Figure IX.F-1. Plot of Estimated Slope and 95% CI by Dose Realization: Any Thyroid Nodule

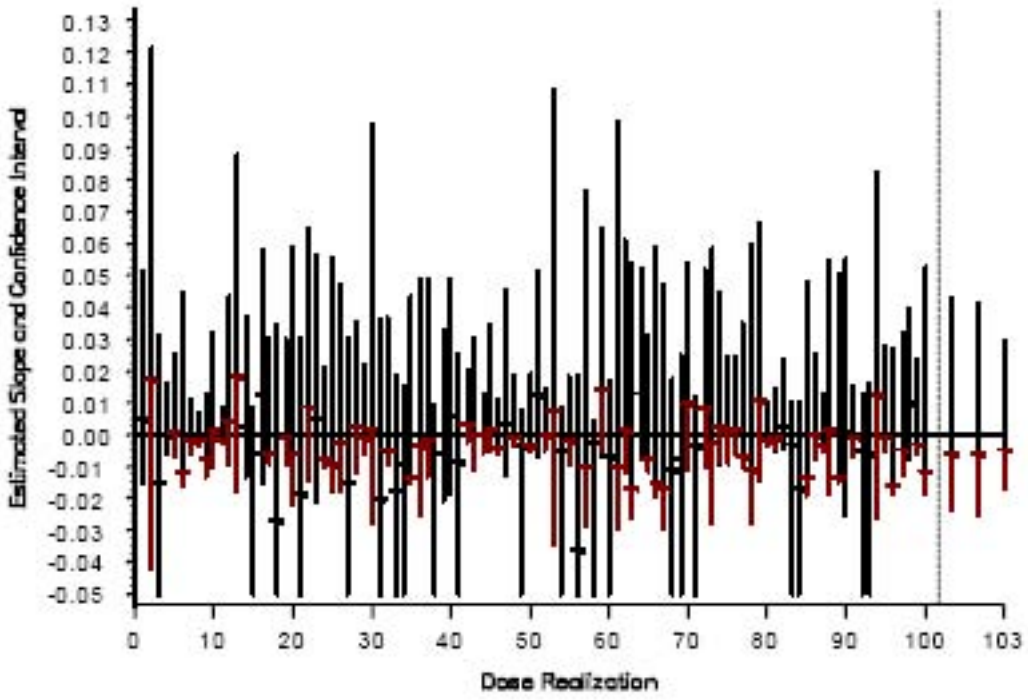
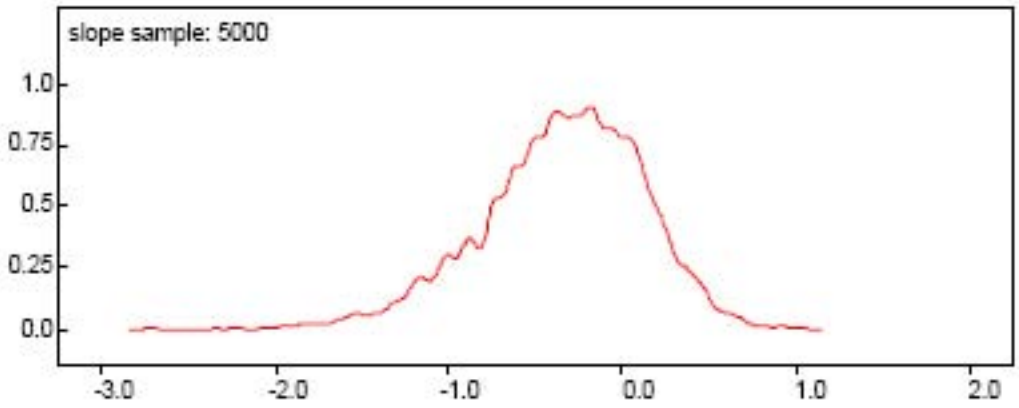


Figure IX.F-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –2.0 and 1.0. The estimate was less than or equal to 0 for 3800 of the 5000 replications, implying an empirical one-tailed p-value of 0.76. The median estimate was –.303 and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –1.65 and 0.62. These may be compared to the estimates of –.09 with confidence interval (–.81, .63) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of any thyroid nodule increased with increasing dose.

Figure IX.F-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Any Thyroid Nodule



G. Hypothyroidism

G.1. Occurrence of Hypothyroidism

The primary and alternative definitions for hypothyroidism were as follows:

- Primary definition: HTDS evaluation or medical records with supporting documentation (267 cases)
- Alternative definition #1: HTDS evaluation or medical records with or without supporting documentation (372 cases)
- Alternative definition #2: HTDS evaluation, any medical records, or inferred from past/current therapy (402 cases)
- Alternative definition #3: Any diagnosis or participant/respondent report (595 cases).

Two hundred and sixty-seven (7.8%) living evaluable participants had a diagnosis of hypothyroidism based on the HTDS evaluation or on medical records with supporting documentation, with 204 (11.7%) women and 63 (3.7%) men having this diagnosis, respectively (Table IX.G-1). An additional 105 (3.1%) living evaluable participants had a diagnosis of hypothyroidism based on medical records but without supporting documentation, and 30 (0.9%) were inferred from past or current therapy. There were 193 (5.6%) reports of hypothyroidism from the participant or his/her CATI respondent.

It should be noted that Alternative definition #1 includes cases from medical records *without* supporting documentation; this category includes many participants who have been treated with thyroid hormone for many years, had normal thyroid function on the HTDS lab evaluation, and yet had no early documentation of an elevated TSH in their medical records. This category therefore very likely includes an unknown number of valid diagnoses for hypothyroidism for which adequate diagnostic information was not available.

Table IX.G-1. Basis for Diagnosis of Hypothyroidism, by Sex

	Female		Male		Total	
Diagnosis of Hypothyroidism	No.	%	No.	%	No.	%
Yes	481	27.5	114	6.7	595	17.3
▪ HTDS evaluation	97	5.6	49	2.9	146	4.2
▪ Medical records *with* supporting documentation	107	6.1	14	0.8	121	3.5
▪ Medical records *without* supporting documentation	91	5.2	14	0.8	105	3.1
▪ Inferred from past/current therapy	27	1.5	3	0.2	30	0.9
▪ Participant/respondent report	159	9.1	34	2.0	193	5.6
No	1250	71.6	1575	93.0	2825	82.1
Unknown	16	0.9	4	0.2	20	0.6
Total	1747	100.0	1693	100.0	3440	100.0

Twenty living evaluable participants were classified as "unknown" with regard to diagnosis of hypothyroidism. These twenty did not have medical record reports of such a diagnosis. Seven of these 20 participants did not have a blood draw, thirteen had participant/respondent report of unknown thyroid disease with 11 taking some kind of medication for this unknown thyroid disease. Therefore, no HTDS evaluation could be made for these twenty participants who were included as non-cases in analyses of the dose-response for hypothyroidism.

Of those with a diagnosis of hypothyroidism, 531 (89.2%) had no known contributing cause (Table IX.G-2). However, among those with a contributing cause, about half were due to thyroid or parathyroid surgery, followed by ^{131}I therapy (21), and lithium therapy (6). Ten participants had some

other contributing cause, with four of the 10 being unknown or uncertain, while two were related to subacute thyroiditis.

Table IX.G-2. Frequency Distribution of Possible Contributing Causes of Hypothyroidism, by Sex

	Female		Male		Total	
Contributing Cause	No.	%	No.	%	No.	%
No Known Contributing Cause	427	88.8	104	91.2	531	89.2
Contributing Cause	54	11.2	10	8.8	64	10.8
^{131}I therapy	20	4.2	1	0.9	21	3.5
Thyroid/parathyroid surgery	25	5.2	5	4.4	30	5.0
Lithium Therapy	4	0.8	2	1.8	6	1.0
Other	8	1.7	2	1.8	10	1.7
Total	481	100.0	114	100.0	595	100.0

Note: A participant can have more than one possible contributing cause

G.1.a. Permanent Hypothyroidism

An additional outcome of hypothyroidism was defined to exclude those with transient hypothyroidism. Transient (temporary) hypothyroidism can occur from certain types of thyroiditis such as viral subacute thyroiditis or postpartum thyroiditis. Transient forms of hypothyroidism usually resolve completely and do not require further treatment. In contrast, permanent hypothyroidism, such as that produced from Hashimoto's thyroiditis, ^{131}I therapy, or thyroid surgery, requires lifelong thyroid hormone replacement. The definition of permanent hypothyroidism included participants with a diagnosis of hypothyroidism based on the HTDS evaluation. Permanent hypothyroidism also included those based on medical records with supporting documentation, excluding those who had a normal TSH value at the time of the HTDS clinic and were not currently on thyroid hormone replacement. Two hundred and fifty seven participants (7.5%) had a diagnosis of permanent hypothyroidism (Table IX.G-3). These cases represented 96% of the cases of hypothyroidism according to the primary definition (i.e., diagnosed from the HTDS evaluation or medical records with supporting documentation).

Table IX.G-3. Permanent Hypothyroidism, by Sex

	Female		Male		Total	
Permanent Hypothyroidism	No.	%	No.	%	No.	%
Yes	196	11.2	61	3.6	257	7.5
No	1551	88.8	1632	96.4	3183	92.6
Total	1747	100.0	1693	100.0	3440	100.0

G.2. Analysis of Hypothyroidism Risk

G.2.a. Primary Analysis

Of the 267 participants with a diagnosis of hypothyroidism based on the HTDS examination or medical records with supporting documentation, 21 were out-of-area participants. The number of cases and proportion with hypothyroidism are shown by sex, in-area status, and dose group in Tables IX.G-4 and IX.G-5.

Table IX.G-4. Diagnoses of Hypothyroidism by Sex, Dose Category, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Medical Record with Supporting Document		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Document		2nd Alternative Definition: Cases Based on HTDS or Medical Record, or Inferred from Medication		3rd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%.	No.	%	No.	%
OOA	125	14	11.2	20	16.0	23	18.4	31	24.8
< 10	182	19	10.4	26	14.3	29	15.9	42	23.1
10-49	320	34	10.6	42	13.1	47	14.7	67	20.9
50-99	313	40	12.8	64	20.4	68	21.7	106	33.9
100-149	220	22	10.0	34	15.5	37	16.8	61	27.7
150-199	126	14	11.1	21	16.7	21	16.7	31	24.6
200-299	139	20	14.4	28	20.1	32	23.0	46	33.1
300-399	144	22	15.3	31	21.5	34	23.6	49	34.0
400-999	171	18	10.5	27	15.8	29	17.0	46	26.9
1000+	7	1	14.3	2	28.6	2	28.6	2	28.6
Total	1747	204	11.7	295	16.9	322	18.4	481	27.5

OOA = out of area participant

B. Male

Thyroid Radiation Dose	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Medical Record with Supporting Document		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Document		2nd Alternative Definition: Cases Based on HTDS or Medical Record, or Inferred from Medication		3rd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%	No.	%	No.	%
OOA	124	7	5.6	7	5.6	8	6.5	10	8.1
< 10	186	8	4.3	10	5.4	10	5.4	13	7.0
10-49	314	10	3.2	12	3.8	13	4.1	18	5.7
50-99	310	11	3.5	12	3.9	12	3.9	19	6.1
100-149	171	7	4.1	8	4.7	8	4.7	12	7.0
150-199	109	2	1.8	2	1.8	2	1.8	5	4.6
200-299	148	7	4.7	8	5.4	8	5.4	11	7.4
300-399	160	7	4.4	10	6.3	10	6.3	13	8.1
400-999	154	4	2.6	7	4.5	8	5.2	11	7.1
1000+	17	0	--	1	5.9	1	5.9	2	11.8
Total	1693	63	3.7	77	4.5	80	4.7	114	6.7

OOA = out of area participant

Table IX.G-5. Additional Disease Outcomes Related to Hypothyroidism by Sex and Estimated Dose (cases based on HTDS examination or medical records with supporting documentation only)

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Permanent Hypothyroidism	
(mGy)	No.	No.	%
OOA	125	14	11.2
< 10	182	18	9.9
10-49	320	34	10.6
50-99	313	36	11.5
100-149	220	20	9.1
150-199	126	14	11.1
200-299	139	19	13.7
300-399	144	22	15.3
400-999	171	18	10.5
1000+	7	1	14.3
Total	1747	196	11.2

B. Male

Thyroid Radiation Dose	Living Evaluable Male	Permanent Hypothyroidism	
(mGy)	No.	No.	%
OOA	124	7	5.6
< 10	186	7	3.8
10-49	314	10	3.2
50-99	310	11	3.5
100-149	171	6	3.5
150-199	109	2	1.8
200-299	148	7	4.7
300-399	160	7	4.4
400-999	154	4	2.6
1000+	17	0	--
Total	1693	61	3.6

OOA = out of area participant

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in row 1 of Table IX.G-6 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, the estimated slope B was slightly less than zero (–0.006 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.016 to 0.047 per Gy, providing no evidence that cumulative incidence increased with increasing dose (one-tailed p = 0.61). The corresponding estimated background rates for diagnosis of benign thyroid nodule were 0.118 with confidence interval (0.097, 0.139) for women and 0.037 with confidence interval (0.023, 0.050) for men. Similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data, although the estimates of the slope were slightly greater than zero: 0.006 per Gy with confidence interval (–0.044, 0.056 per Gy) with ungrouped data, and 0.002 per Gy with confidence interval (–0.055, 0.060 per Gy) with grouped data (Table IX.G-6, rows 2 and 3 respectively).

Table IX.G-6. Dose-Response Results for Diagnoses of Hypothyroidism

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation or medical record with documentation)	Linear	Primary	None	MLE	.118 ± .009 (.097, .139)	.037 ± .006 (.023, .050)	–.006 ± .019 (< –.016, .047)	0.61
2.	Primary definition	Linear	Primary	None	LSU	.116 ± .008 (.098, .134)	.035 ± .008 (.016, .053)	.006 ± .021 (–.044, .056)	0.39
3.	Primary definition	Linear	Primary	None	LSG	.117 ± .008 (.098, .135)	.035 ± .008 (.016, .054)	.002 ± .024 (–.055, .060)	0.46
4.	Alternative def. #1 (HTDS evaluation or medical records with or without documentation)	Linear	Primary	None	MLE	.165 ± .010 (.141, .189)	.040 ± .006 (.025, .055)	.026 ± .023 (< -.020, .086)	0.12
5.	Alternative def. #2 (HTDS evaluation or medical record, or inferred from medication	Linear	Primary	None	MLE	.180 ± .010 (.155, .205)	.042 ± .006 (.026, .057)	.025 ± .024 (< -.020, .087)	0.13

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.G-6. Dose-Response Results for Diagnoses of Hypothyroidism (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Alternative def. #3 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.271 ± .012 (.242, .300)	.060 ± .008 (.042, .078)	.038 ± .028 (-.023, .108)	0.076
7.	Permanent hypothyroidism	Linear	Primary	None	MLE	.112 ± .009 (.092, .133)	.035 ± .006 (.021, .048)	-.001 ± .020 (< -.015, .053)	0.52
8.	Primary definition	LQ	Primary	None	LSU	.117 ± .008 (.097, .138)	.036 ± .008 (.015, .057)	Lin: –.006 ± .035 (–.094, .082) Quad: .010 ± .023 (–.049, .068)	Quad: 0.68
9.	Primary definition	Logistic	Primary	None	MLE	.116 (.095, .140)	.035 (.025, .049)	.08 ± .29 (-.62, .78)	0.39

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.G-6. Dose-Response Results for Diagnoses of Hypothyroidism (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
10.	Alternative def. #1	Logistic	Primary	None	MLE	.161 (.137, .188)	.042 (.031, .056)	.37 ± .23 (-.19, .93)	0.065
11.	Alternative def. #2	Logistic	Primary	None	MLE	.176 (.151, .204)	.043 (.032, .058)	.34 ± .23 (-.22, .89)	0.08
12.	Alternative def. #3	Logistic	Primary	None	MLE	.266 (.236, .298)	.062 (.049, .080)	.33 ± .21 (-.16, .83)	0.055
13.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.117 ± .009 (.096, .139)	.036 ± .006 (.022, .051)	-.002 ± .023 (< -.047, .060)	0.53
14.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.113± .010 (.089,.136)	.032 ± .006 (.017, .047)	.047 ± .041 (-.045, .151)	0.12

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.G-6. Dose-Response Results for Diagnoses of Hypothyroidism (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
15.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.115 ± .009 (.093, .138)	.031 ± .006 (.017, .045)	.004 ± .021 (<-.014, .060)	0.42
16.	Primary definition	Linear	Alt. #1	None	MLE	.120 ± .009 (.098, .141)	.038 ± .006 (.024, .051)	-.011 ± .017 (< -.016, .037)	0.74
17.	Primary definition	Linear	Alt. #2	None	MLE	.117 ± .009 (.096, .138)	.036 ± .006 (.022, .050)	.0002 ± .020 (< -.017, .053)	0.50
18.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.118 ± .008 (.098, .138)	.038 ± .005 (.025, .051)	-.008 ± .019 (< -.016, .044)	0.66
19.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.118 ± .008 (.098, .138)	.039 ± .005 (.026, .052)	-.010 ± .018 (< -.016, >.041)	0.69

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

G.2.b. Alternative Definitions for Diagnosis of Hypothyroidism

Each of the three alternative definitions of hypothyroidism (section IX.G.1. above) added substantial numbers of cases.

Parameter estimates for the linear dose-response model are shown in rows 4 and 5 of Table IX.G-6 above for each of the three alternative definitions of hypothyroidism. For none of the three alternative definitions was there a clearly statistically significant increase of cumulative incidence with increasing dose.

G.2.c. Permanent Hypothyroidism

In the analyses described above, participants with transient hypothyroidism were included among the cases. An additional analysis was performed in which participants with transient hypothyroidism only were excluded from the cases. The results are shown in row 7 of Table IX.G-6 above. The cumulative incidence of permanent hypothyroidism decreased slightly with increasing dose, with an estimated slope of –0.001 per Gy and confidence interval ranging from less than –0.015 to 0.053 per Gy ($p = 0.52$).

G.2.d. Alternative Dose-Response Functions

As shown in row 8 of Table IX.G-6, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.010 with Bonferroni-adjusted 95% confidence interval ranging from –0.049 to 0.068. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.68$).

In the analysis of hypothyroidism based on the HTDS or medical records with supporting documentation, i.e., the primary criterion for defining cases with hypothyroidism, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.08, with Bonferroni-adjusted 95% confidence limits ranging from –0.62 to 0.78 (Table IX.G-6, row 9). Thus in the primary analysis of hypothyroidism, there was no evidence from the logistic regression model that cumulative incidence increased significantly with increasing dose ($p = 0.39$). However in logistic regression analyses using the alternative criteria for defining cases with hypothyroidism, the estimated regression coefficients were larger but did not achieve statistical significance (see rows 10, 11 and 12 of Table IX.G-6).

G.2.e. Effect of Excluding Participants in High Dose Categories

When those with an estimated dose > 1000 mGy were excluded, the estimated slope B was –0.002 per Gy with Bonferroni-adjusted 95% confidence interval ranging from less than –0.047 to 0.060 per Gy, providing no evidence that the cumulative incidence of hypothyroidism increased with increasing dose ($p = 0.53$; Table IX.G-6, row 13). When participants with estimated dose > 400 mGy were excluded, the estimated slope was 0.047 per Gy with confidence interval ranging from –0.045 to 0.151 per Gy, and there was no evidence that the cumulative incidence increased with increasing dose ($p = 0.12$; Table IX.G-6, row 14).

G.2.f. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When Okanogan and Ferry/Stevens geostrata were excluded from the analyses, the estimated slope of the dose-response increased from –0.006 per Gy to the slightly positive value of 0.004 per Gy,

with confidence interval ranging from less than –0.014 to 0.060 per Gy (Table IX.G-6, row 15). Thus the cumulative incidence of hypothyroidism did not increase significantly with increasing dose (p = 0.42).

G.2.g. Analysis of Hypothyroidism in Relation to Alternative Dose Estimates

In the analysis using the first set of alternative dose estimates (Table IX.G-6, row 16), the estimated slope B was –0.011 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than -0.016 to 0.037 per Gy, providing no evidence that the cumulative incidence of hypothyroidism increased with increasing dose (p = 0.74). The results for the second set of alternative dose estimates were similar (Table IX.G-6, row 17), with an estimated slope B of 0.0002 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than -0.017 to 0.053 per Gy, providing no evidence that the cumulative incidence increased with increasing dose (p = 0.50).

G.2.h. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 18 and 19 of Table IX.G-6, in both analyses the inclusion of the out-of-area participants slightly decreased the estimated slope of the dose-response, but did not materially change the dose-response results. In particular, the estimated slope of the dose-response was slightly negative in both scoping analyses, providing no evidence that cumulative incidence increased with increasing dose.

G.2.i. Analysis of Hypothyroidism in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

G.2.i.1. Analysis by Geostratum

The proportions of women with hypothyroidism (HTDS or medical record with documentation) ranged from 11/75 (14.7%) in the Okanogan geostratum to 15/165 (9.1%) in the Adams geostratum (Table IX.G-7). For men they ranged from 7/70 (10.0%) in the Ferry/Stevens geostratum to 8/501 (1.6%) in the Pasco/Kennewick geostratum. However the heterogeneity among the nine geostrata was not statistically significant (p = 0.51). Hypothyroidism was somewhat more common in the Okanogan and Ferry/Stevens geostrata (13.3% and 8.2% for women and men, respectively) compared to the other geostrata (11.5% and 3.3%, respectively), but this difference was not statistically significant (p = 0.12).

Table IX.G-7. Diagnoses of Hypothyroidism Based on the HTDS Evaluation or on Medical Records with Supporting Documentation

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	21	11.7	173	7	4.0	352	28	8.0
Pasco/Kennewick	508	58	11.4	501	8	1.6	1009	66	6.5
Benton County	376	45	12.0	358	16	4.5	734	61	8.3
Franklin County	73	10	13.7	76	6	7.9	149	16	10.7
Adams County	165	15	9.1	156	5	3.2	321	20	6.2
Walla Walla (city)	133	16	12.0	131	3	2.3	264	19	7.2
Walla Walla County	170	20	11.8	164	7	4.3	334	27	8.1
Okanogan County	75	11	14.7	64	4	6.3	139	15	10.8
Ferry/Stevens Counties	68	8	11.8	70	7	10.0	138	15	10.9
Total	1747	204	11.7	1693	63	3.7	3440	267	7.8

Because of the large numbers of cases added by the alternative criteria for defining cases of hypothyroidism (see IX.G-1 above), results for the alternative definitions of hypothyroidism are also presented (Tables IX.G-8 to IX.G-10, below). Generally, similar degrees of heterogeneity among the geostrata were observed in the analyses using the alternative definitions as compared to the primary definition, ($p = 0.57$, $p = 0.55$, and $p = 0.017$ for the first, second and third alternative definitions, respectively). Only when diagnoses that were reported by participants or CATI respondents but not confirmed by the HTDS evaluation were included (Table IX.G-10) was there evidence of significant heterogeneity among geostrata. The tendency toward higher proportions of cases in the Okanogan and Ferry/Stevens geostrata was observed in all three alternatives.

Table IX.G-8. Diagnoses of Hypothyroidism Based on the HTDS Evaluation or Medical Records with or without Supporting Documentation (1st Alternative Definition), by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	28	15.6	173	7	4.0	352	35	9.9
Pasco/Kennewick	508	87	17.1	501	15	3.0	1009	102	10.1
Benton County	376	60	16.0	358	16	4.5	734	76	10.4
Franklin County	73	13	17.8	76	6	7.9	149	19	12.8
Adams County	165	27	16.4	156	6	3.8	321	33	10.3
Walla Walla (city)	133	20	15.0	131	5	3.8	264	25	9.5
Walla Walla County	170	32	18.8	164	9	5.5	334	41	12.3
Okanogan County	75	17	22.7	64	5	7.8	139	22	15.8
Ferry/Stevens Counties	68	11	16.2	70	8	11.4	138	19	13.8
Total	1747	295	16.9	1693	77	4.5	3440	372	10.8

Table IX.G-9. Diagnoses of Hypothyroidism Based on the HTDS Evaluation, or on Medical Records with or without Supporting Documentation (2nd Alternative Definition), or Inferred from Past/Current Therapy, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	30	16.8	173	7	4.0	352	37	10.5
Pasco/Kennewick	508	95	18.7	501	16	3.2	1009	111	11.0
Benton County	376	65	17.3	358	18	5.0	734	83	11.3
Franklin County	73	14	19.2	76	6	7.9	149	20	13.4
Adams County	165	29	17.6	156	6	3.8	321	35	10.9
Walla Walla (city)	133	23	17.3	131	5	3.8	264	28	10.6
Walla Walla County	170	34	20.0	164	9	5.5	334	43	12.9
Okanogan County	75	19	25.3	64	5	7.8	139	24	17.3
Ferry/Stevens Counties	68	13	19.1	70	8	11.4	138	21	15.2
Total	1747	322	18.4	1693	80	4.7	3440	402	11.7

Table IX.G-10. Diagnoses of Hypothyroidism Based on Any Source (3rd Alternative Definition), by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	47	26.3	173	10	5.8	352	57	16.2
Pasco/Kennewick	508	135	26.6	501	24	4.8	1009	159	15.8
Benton County	376	94	25.0	358	24	6.7	734	118	16.1
Franklin County	73	27	37.0	76	8	10.5	149	35	23.5
Adams County	165	41	24.8	156	8	5.1	321	49	15.3
Walla Walla (city)	133	39	29.3	131	8	6.1	264	47	17.8
Walla Walla County	170	55	32.4	164	16	9.8	334	71	21.3
Okanogan County	75	23	30.7	64	7	10.9	139	30	21.6
Ferry/Stevens Counties	68	20	29.4	70	9	12.9	138	29	21.0
Total	1747	481	27.5	1693	114	6.7	3440	595	17.3

G.2.i.2. Analysis by Dichotomous Exposure Variable

A total of 96 (7.6%) of the 1257 participants included in these analyses had a diagnosis of hypothyroidism based on the HTDS examination or a medical record with supporting documentation (see Table IX.G-11). These included 35/580 (6.0%) in the high exposure group and 61/677 (9.0%) in the low exposure group. Thus there was no evidence that the cumulative incidence of hypothyroidism was significantly higher in the high exposure group ($p = 0.97$).

Table IX.G-11. Diagnoses of Hypothyroidism Based on HTDS or Medical Record with Supporting Documentation, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	40	11.4	326	21	6.4	677	61	9.0
High	298	31	10.4	282	4	1.4	580	35	6.0
Total	649	71	10.9	608	25	4.1	1257	96	7.6

Because of the large numbers of cases added by the three alternative definitions for hypothyroidism (see section IX.G.1 above), results for these alternatives are also presented briefly. The first alternative definition added 41 cases with diagnoses based on medical records without supporting documentation, for a total of 137 (10.9%). The second alternative added 11 cases with diagnoses inferred from medication, for a total of 148 (11.8%). The third alternative added 60 further cases with diagnoses reported by the participant or his/her CATI respondent, for a total of 208 (16.5%). In none of the alternative analyses was the cumulative incidence of hypothyroidism found to be elevated in the high exposure group ($p = 0.86$, 0.94, and 0.73 for the first, second, and third alternatives, respectively).

G.2.j. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of hypothyroidism, i.e., those based on the HTDS evaluation or on medical records with supporting documentation, and on the primary dose estimates. Table IX.G-12 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type. Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. It is evident from Table IX.G-12 that the model was not significantly improved by adjusting for any of the other factors as a potential confounder: none produced a significantly better fit to the data. Since the estimated slope was virtually unaffected by such adjustments, it does not appear that omitting these factors introduces any important bias in the dose-response results.

Table IX.G-12. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid, and Interview Type: Hypothyroidism

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	.082 ± .293 (–.620, .785)	Not Applicable	–.508 ± .704 (–2.27, 1.25)	.240 ± .321 (–.563, 1.04)	.31
Prenatal exposure?	1034 / 3191	.082 ± .293 (–.620, .785)	.063 ± .297 (–.702, .829)	.023 ± .346 (–.891, .936)	.187 ± .589 (–1.37, 1.74)	.81
1st exposure before age 180 days?	1478 / 3191	.082 ± .293 (–.620, .785)	.097 ± .297 (–.669, .863)	–.630 ± .568 (–2.14, .859)	.386 ± .317 (–.451, 1.22)	.11
Age at exam >50?	2001 / 3191	.082 ± .293 (–.620, .785)	.149 ± .292 (–.604, .902)	.369 ± .445 (–.805, 1.54)	.004 ± .386 (–1.01, 1.02)	.54
NTS ^{131}I dose > 5.3 mGy?	1563 / 3181	.084 ± .297 (–.627, .795)	.002 ± .311 (–.800, .804)	–.184 ± .422 (–1.30, .929)	.248 ± .445 (–.925, 1.42)	.49
History of any cancer other than thyroid?	248 / 3186	.083 ± .293 (–.620, .785)	.081 ± .293 (–.674, .836)	.043 ± .330 (–.828, .914)	.224 ± .614 (–1.40, 1.84)	.80
Expanded In-Person Interview?	1212 / 3191	.082 ± .293 (–.620, .785)	.119 ± .298 (–.648, .885)	–.603 ± .541 (–2.03, .826)	.456 ± .325 (–.402, 1.31)	.089

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.G-13 and IX.G-14 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposures as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for hypothyroidism.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.G-13 and IX.G-14.

Table IX.G-13. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Hypothyroidism

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
CAT scan of the upper body?	775 / 3149	.046 ± .297 (–.664, .757)	.034 ± .299 (–.736, .803)	–.044 ± .342 (–.945, .857)	.356 ± .675 (–1.42, 2.14)	.60
Diagnostic x-rays of the head?	1191 / 3155	.083 ± .296 (–.625, .791)	.080 ± .296 (–.684, .843)	.103 ± .362 (–.852, 1.06)	.033 ± .514 (–1.32, 1.39)	.91
Diagnostic x-rays of the neck?	966 / 3167	.059 ± .297 (–.652, .770)	.070 ± .296 (–.692, .832)	–.264 ± .437 (–1.42, .888)	.375 ± .376 (–.616, 1.37)	.27
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	.080 ± .294 (–.624, .784)	.090 ± .294 (–.667, .847)	.907 ± 1.22 (–2.31, 4.12)	.047 ± .305 (–.757, .852)	.52
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	.102 ± .294 (–.603, .807)	.099 ± .295 (–.660, .858)	–.087 ± .353 (–1.02, .843)	.678 ± .554 (–.785, 2.14)	.26
Barium enema?	825 / 3159	.085 ± .295 (–.622, .792)	.084 ± .295 (–.677, .845)	.272 ± .329 (–.595, 1.14)	–.495 ± .658 (–2.23, 1.24)	.28
Upper GI?	1146 / 3177	.066 ± .296 (–.642, .773)	.066 ± .295 (–.695, .827)	.146 ± .357 (–.796, 1.09)	–.090 ± .519 (–1.46, 1.28)	.71
Intravenous pyelogram?	398 / 3157	.007 ± .304 (–.721, .734)	.013 ± .304 (–.770, .796)	–.101 ± .337 (–.990, .788)	.804 ± .824 (–1.37, 2.98)	.32
Fluoroscopy of the upper body?	246 / 3161	.072 ± .295 (–.635, .779)	.078 ± .295 (–.682, .839)	.094 ± .304 (–.707, .895)	–.154 ± 1.19 (–3.28, 2.97)	.84
Nuclear scan (excluding thyroid scan)?	217 / 3162	.089 ± .292 (–.611, .789)	.098 ± .292 (–.653, .849)	.137 ± .293 (–.636, .909)	–1.19 ± 1.89 (–6.17, 3.80)	.46
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	.082 ± .293 (–.620, .785)	.083 ± .294 (–.674, .839)	–.372 ± .493 (–1.67, .930)	.391 ± .357 (–.551, 1.33)	.20

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.G-14. Confounding and Effect Modification by Occupational History: Hypothyroidism

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification: Group 0	Including Effect Modification: Group 1	P
Any metal industry?	238 / 3191	.082 ± .293 (–.620, .785)	.082 ± .293 (–.673, .838)	.154 ± .290 (–.611, .920)	–3.53 ± 2.83 (–11.0, 3.94)	.11
Any nuclear facility?	371 / 3191	.082 ± .293 (–.620, .785)	.071 ± .297 (–.695, .837)	.103 ± .315 (–.729, .935)	–.158 ± .871 (–2.45, 2.14)	.77
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	.082 ± .293 (–.620, .785)	.081 ± .294 (–.676, .838)	.164 ± .314 (–.665, .992)	–.476 ± .965 (–3.02, 2.07)	.49
Any of the above industries or occupations?	892 / 3191	.082 ± .293 (–.620, .785)	.079 ± .294 (–.678, .837)	.295 ± .326 (–.566, 1.16)	–.617 ± .686 (–2.43, 1.19)	.20

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.G-15 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.G-15. Confounding and Effect Modification by Smoking: Hypothyroidism

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification: Group 0	Including Effect Modification: Group 1	P
Cigarettes (unfiltered or filtered)?	1854 / 3183	.086 ± .294 (–.617, .790)	.099 ± .296 (–.663, .860)	.078 ± .474 (–1.17, 1.33)	.112 ± .377 (–.883, 1.11)	.96
Any of cigarettes, cigar or pipe?	1900 / 3183	.086 ± .294 (–.617, .790)	.098 ± .296 (–.663, .860)	.071 ± .476 (–1.18, 1.33)	.116 ± .376 (–.875, 1.11)	.94

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

G.2.k. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for hypothyroidism are shown in Figure IX.G-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 32 of the 100 realizations, the confidence interval

includes 0 for all 100 realizations. Also shown in Figure IX.G-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for the majority of realizations the estimated slope was less than 0.

Figure IX.G-1 Plot of Estimated Slope and 95% CI by Dose Realization: Hypothyroidism

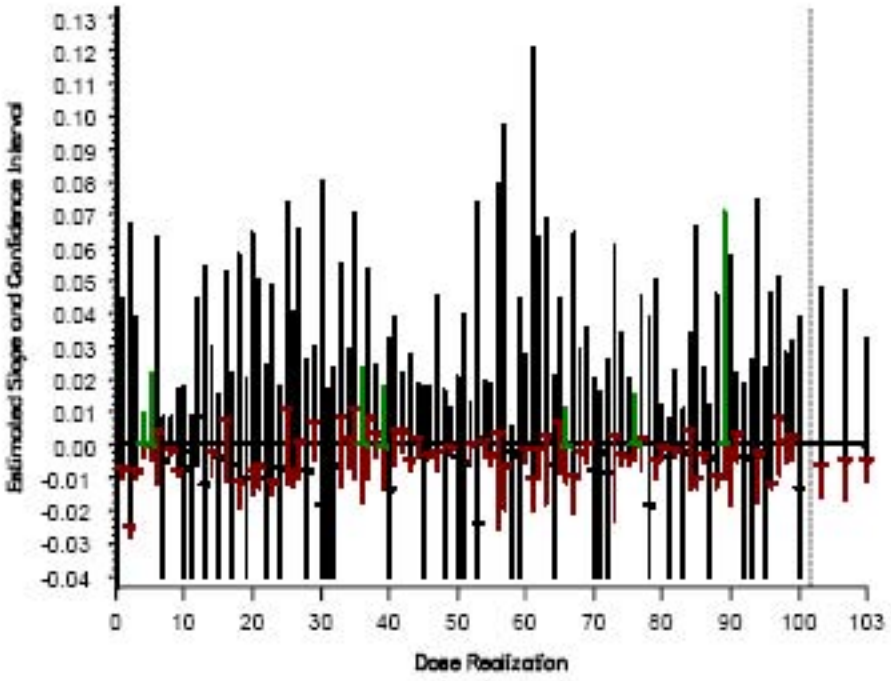
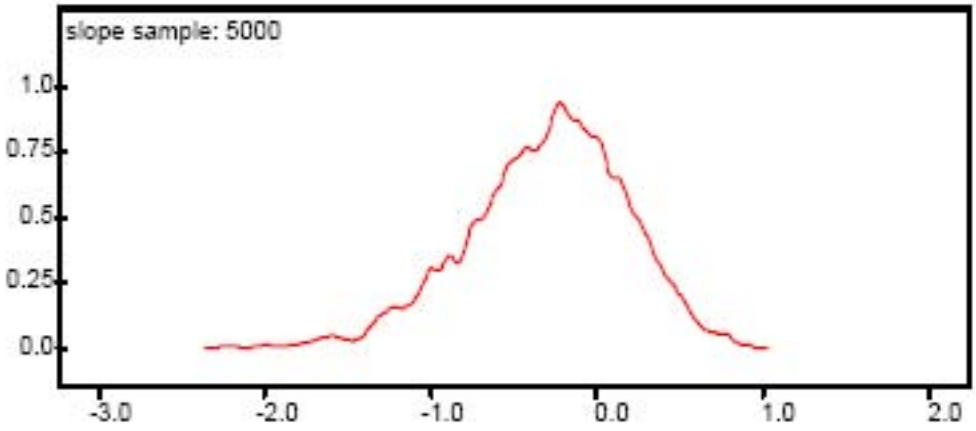


Figure IX.G-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –2.0 and 1.0. The estimate was less than or equal to 0 for 2368 of the 5000 replications, implying an empirical one-tailed p-value of 0.47. The median estimate was 0.028, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –1.40 and 0.86. These may be compared to the estimates of –.08 with confidence interval (–0.62, 0.78) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of hypothyroidism increased with increasing dose.

Figure IX.G-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Hypothyroidism



H. Autoimmune (Hashimoto's) Thyroiditis

H.1. Occurrence of Autoimmune (Hashimoto's) Thyroiditis

The primary and alternative definitions for autoimmune (Hashimoto's) thyroiditis were as follows:

- Primary definition: HTDS evaluation or medical records with supporting documentation (625 cases)
- Alternative definition #1: HTDS evaluation or medical records with or without supporting documentation (628 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (629 cases).

Of the 3440 living evaluable participants, 629 (18.3%) had diagnoses of autoimmune thyroiditis (Table IX.H-1), with all but four based on the HTDS evaluation or medical records with supporting documentation.

Table IX.H-1. Basis for Diagnosis of Autoimmune Thyroiditis, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	407	23.3	222	13.1	629	18.3
▪ HTDS evaluation	402	23.0	221	13.1	623	18.1
▪ Medical records with supporting documentation	1	0.1	1	0.1	2	0.1
▪ Medical records *without* supporting documentation	3	0.2	0	--	3	0.1
▪ Participant/respondent report	1	0.1	0	--	1	0.0
No	1333	76.3	1469	86.8	2802	81.5
Unknown	7	0.4	2	0.1	9	0.3
Total	1747	100.0	1693	100.0	3440	100.0

Nine living evaluable participants were classified as "unknown" with regard to diagnosis of autoimmune thyroiditis. These nine did not have medical record or participant/respondent reports of such diagnoses, and did not have a blood draw (8) or had an insufficient quantity of blood drawn to perform the AMA or anti-TPO test (1) and therefore no HTDS evaluation could be made. These nine participants were included as non-cases in analyses of the dose-response for autoimmune thyroiditis.

H.1.a. Additional Outcomes Related to Assay for Anti-Thyroid Immune Response

Late in the course of the study, it was decided to assay anti-thyroid globulin antibody (anti-TG) levels in the serum specimens that had been provided by nearly all study participants and stored in frozen form. The anti-TG test, although not considered to be the best test of autoimmune thyroiditis, provides an additional marker of antithyroid immune response. This made it possible to define additional outcomes of autoimmune thyroiditis based on the combined results of AMA/anti-TPO and anti-TG, or on anti-TG alone. Two additional outcomes were defined:

- Positive antibodies on the AMA/anti-TPO and/or the anti-TG test. A total of 779 living evaluable participants were antibody-positive based on either or both of their AMA/anti-TPO results and their anti-TG results or had a diagnosis of autoimmune thyroiditis based on medical records with supporting documentation. These 779 comprised 22.6% of the 3440 living evaluable participants (Table IX.H-2).

- Positive antibodies on the anti-TG test, without regard to the AMA/anti-TPO results or a diagnosis of autoimmune thryoiditis based on medical records with supporting documentation. A total of 507

living evaluable participants met these criteria and comprised 14.7% of the 3440 living evaluable participants (Table IX.H-3).

Table IX.H-2. Diagnosis of Autoimmune Thyroiditis Based on AMA/anti-TPO and/or anti-TG, or Medical Records with Supporting Documentation, by Sex

	Female		Male		Total	
Autoimmune Thyroiditis	No.	%	No.	%	No.	%
Yes	500	28.6	279	16.5	779	22.6
No	1247	71.4	1414	83.5	2661	77.4
Total	1747	100.0	1693	100.0	3440	100.0

Table IX.H-3. Diagnosis of Autoimmune Thyroiditis Based on anti-TG, or Medical Records with Supporting Documentation, by Sex

	Female		Male		Total	
Autoimmune Thyroiditis	No.	%	No.	%	No.	%
Yes	327	18.7	180	10.6	507	14.7
No	1420	81.3	1513	89.4	2933	85.3
Total	1747	100.0	1693	100.0	3440	100.0

H.1.b. Additional Outcomes Related to Autoimmune Thyroiditis and Hypothyroidism

Two additional outcomes of autoimmune thyroiditis in combination with hypothyroidism were defined to narrow the definition of autoimmune thyroiditis to include both an immune marker for autoimmune thyroid disease and hypothyroidism. These outcomes would represent the most advanced stages of the autoimmune process (hypothyroidism). These additional outcomes were added to determine if a dose-response might be seen with these most advanced stages but missed in the broader category of autoimmune thyroiditis where hypothyroidism had not yet occurred. For this purpose, the diagnoses of autoimmune thyroiditis and hypothyroidism in these additional outcomes were based on the primary definitions, i.e., on the HTDS evaluation or medical records with supporting documentation. The two additional outcomes were:

- Autoimmune thyroiditis (positive AMA/anti-TPO) in participants who also had a diagnosis of hypothyroidism. There were 175 (5.1%) such cases (Table IX.H-4).

- Autoimmune thyroiditis (positive AMA/anti-TPO) in participants who also had a diagnosis of non-iatrogenic, permanent hypothyroidism. This outcome was similar to the first, but excluded those with an iatrogenic cause of hypothyroidism (surgery or ^{131}I therapy) or with transient hypothyroidism. One hundred and sixty-one (4.7%) living evaluable participants met this definition (Table IX.H-5).

Table IX.H-4. Cross-tabulation of Disease Status with Respect to Diagnosis of Autoimmune Thyroiditis in combination with Hypothyroidism, by Sex

Autoimmune Thyroiditis	Female		Male		Total	
with Hypothyroidism	No.	%	No.	%	No.	%
Yes	135	7.7	40	2.4	175	5.1
No	1612	92.3	1653	97.6	3265	94.9
Total	1747	100.0	1693	100.0	3440	100.0

Table IX.H-5. Autoimmune Thyroiditis in Combination with Non-Iatrogenic, Permanent Hypothyroidism, by Sex

Autoimmune Thyroiditis with	Female		Male		Total	
Non-iatrogenic Hypothyroidism	No.	%	No.	%	No.	%
Yes	122	7.0	39	2.3	161	4.7
No	1625	93.0	1654	97.7	3279	95.3
Total	1747	100.0	1693	100.0	3440	100.0

H.2. Analysis of Autoimmune (Hashimoto's) Thyroiditis Risk

H.2.a. Primary Analysis

Of the 625 participants with a diagnosis of autoimmune thyroiditis based on the HTDS examination or medical records with supporting documentation, 43 were out-of-area participants for whom the CIDER program could not calculate dose estimates. The proportions with autoimmune thyroiditis according to the primary and two alternative definitions are shown by sex, dose category and basis for diagnosis in Table IX.H-6.

Table IX.H-6. Diagnoses of Autoimmune (Hashimoto's) Thyroiditis by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	125	22	17.6	22	17.6	22	17.6
< 10	182	44	24.2	44	24.2	45	24.7
10-49	320	71	22.2	71	22.2	71	22.2
50-99	313	81	25.9	82	26.2	82	26.2
100-149	220	53	24.1	54	24.5	54	24.5
150-199	126	36	28.6	36	28.6	36	28.6
200-299	139	29	20.9	29	20.9	29	20.9
300-399	144	33	22.9	34	23.6	34	23.6
400-999	171	32	18.7	32	18.7	32	18.7
1000+	7	2	28.6	2	28.6	2	28.6
Total	1747	403	23.1	406	23.2	407	23.3

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	124	21	16.9	21	16.9	21	16.9
< 10	186	26	14.0	26	14.0	26	14.0
10-49	314	40	12.7	40	12.7	40	12.7
50-99	310	47	15.2	47	15.2	47	15.2
100-149	171	17	9.9	17	9.9	17	9.9
150-199	109	12	11.0	12	11.0	12	11.0
200-299	148	18	12.2	18	12.2	18	12.2
300-399	160	20	12.5	20	12.5	20	12.5
400-999	154	20	13.0	20	13.0	20	13.0
1000+	17	1	5.9	1	5.9	1	5.9
Total	1693	222	13.1	222	13.1	222	13.1

Table IX.H-7 displays the numbers of participants with diagnoses of autoimmune thyroiditis when anti-TG was used in addition to AMA/anti-TPO to identify antithyroid immune response, or when anti-TG was used alone.

Table IX.H-7. Additional Disease Outcomes Related to Autoimmune Thyroiditis by Sex and Estimated Dose (cases based on HTDS examination or medical records with supporting documentation only)

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	HTDS Diagnosis from AMA/anti-TPO and/or anti-TG, or Medical Record with Supporting Documentation		HTDS Diagnosis from anti-TG, or Medical Record with Supporting Documentation	
	No.	No.	%	No.	%
Out of Area	125	25	20.0	13	10.4
< 10	182	62	34.1	45	24.7
10-49	320	91	28.4	57	17.8
50-99	313	89	28.4	49	15.7
100-149	220	72	32.7	57	25.9
150-199	126	42	33.3	27	21.4
200-299	139	35	25.2	24	17.3
300-399	144	38	26.4	28	19.4
400-999	171	44	25.7	25	14.6
1000+	7	2	28.6	2	28.6
Total	1747	500	28.6	327	18.7

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	HTDS Diagnosis from AMA/anti-TPO and/or anti-TG, or Medical Record with Supporting Documentation		HTDS Diagnosis from anti-TG, or Medical Record with Supporting Documentation	
	No.	No.	%	No.	%
Out of Area	124	26	21.0	20	16.1
< 10	186	33	17.7	26	14.0
10-49	314	51	16.2	29	9.2
50-99	310	58	18.7	35	11.3
100-149	171	21	12.3	13	7.6
150-199	109	17	15.6	10	9.2
200-299	148	24	16.2	18	12.2
300-399	160	24	15.0	16	10.0
400-999	154	24	15.6	13	8.4
1000+	17	1	5.9	0	--
Total	1693	279	16.5	180	10.6

Table IX.H-8 displays the numbers of participants with diagnoses of autoimmune thyroiditis together with diagnoses of hypothyroidism.

Table IX.H-8. Disease Outcomes Related to Autoimmune Thyroiditis with Hypothyroidism by Sex and Estimated Dose (cases based on HTDS examination or medical records with supporting documentation only)

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Autoimmune Thyroiditis with Any Hypothyroidism		Autoimmune Thyroiditis with Non-Iatrogenic, Permanent Hypothyroidism	
	No.	No.	%	No.	%
Out of Area	125	10	8.0	9	7.2
< 10	182	14	7.7	12	6.6
10-49	320	25	7.8	22	6.9
50-99	313	27	8.6	23	7.3
100-149	220	11	5.0	10	4.5
150-199	126	10	7.9	10	7.9
200-299	139	14	10.1	13	9.4
300-399	144	13	9.0	12	8.3
400-999	171	10	5.8	10	5.8
1000+	7	1	14.3	1	14.3
Total	1747	135	7.7	122	7.0

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Autoimmune Thyroiditis with Any Hypothyroidism		Autoimmune Thyroiditis with Non-Iatrogenic, Permanent Hypothyroidism	
	No.	No.	%	No.	%
Out of Area	124	5	4.0	5	4.0
< 10	186	4	2.2	4	2.2
10-49	314	6	1.9	6	1.9
50-99	310	8	2.6	8	2.6
100-149	171	3	1.8	3	1.8
150-199	109	1	0.9	1	0.9
200-299	148	4	2.7	4	2.7
300-399	160	5	3.1	5	3.1
400-999	154	4	2.6	3	1.9
1000+	17	0	--	0	--
Total	1693	40	2.4	39	2.3

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.H-9 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope of the dose-response was slightly less than zero (–0.026 per Gy; row 1 of Table IX.H-9) with Bonferroni-adjusted 95% confidence interval ranging from less than –0.057 to 0.044 per Gy, providing no evidence that cumulative incidence increased with increasing dose ($p = 0.82$). The corresponding estimated background rates for diagnosis of benign thyroid nodule were 0.239 with confidence interval (0.212, 0.267) for women and 0.133 with confidence interval (0.109, 0.156) for men. Very similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data (Table IX.H-9, rows 2 and 3).

Table IX.H-9. Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroiditis

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation or medical record with documentation)	Linear	Primary	None	MLE	.239 ± .012 (.212, .267)	.133 ± .010 (.109, .156)	–.026 ± .026 (< –.057, .044)	0.82
2.	Primary definition	Linear	Primary	None	LSU	.240 ± .011 (.214, .266)	.133 ± .011 (.107, .160)	–.029 ± .030 (–.102, .043)	0.83
3.	Primary definition	Linear	Primary	None	LSG	.243 ± .011 (.216, .270)	.137 ± .012 (.109, .164)	–.048 ± .035 (–.131, .035)	0.92
4.	Alternative def. #1 (HTDS or medical record with or without documentation)	Linear	Primary	None	MLE	.241 ± .012 (.213, .269)	.133 ± .010 (.109, .156)	–.025 ± .026 (< –.057, .044)	0.82
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.242 ± .012 (.214, .269)	.133 ± .010 (.109, .156)	–.026 ± .026 (< –.057, .044)	0.83
6.	Diagnoses based on AMA/anti-TPO and/or anti-TG	Linear	Primary	None	MLE	.300 ± .012 (.270, .329)	.168 ± .011 (.143, .194)	–.039 ± .029 (< –.071, .036)	0.90

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.H-9. Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroiditis (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
7.	Diagnoses based on anti-TG, without regard to AMA/anti-TPO	Linear	Primary	None	MLE	.199 ± .011 (.174, .225)	.107 ± .009 (.087, .128)	–.032 ± .022 (< –.045, .030)	0.90
8.	Autoimmune thyroiditis with any hypothyroidism	Linear	Primary	None	MLE	.077 ± .007 (.060, .094)	.022 ± .005 (.011, .033)	.000 ± .015 (< –.010, >.015)	0.50
9.	Autoimmune thyroiditis with non-iatrogenic, permanent hypothyroidism	Linear	Primary	None	MLE	.070 ± .007 (.053, .086)	.022 ± .004 (.011, .032)	.001 ± .015 (< –.010, .043)	0.48
10.	Primary definition	LQ	Primary	None	LSU	.246 ± .012 (.217, .276)	.140 ± .012 (.110, .170)	Lin: –.090 ± .051 (–.218, .038) Quad: .050 ± .034 (–.035, .134)	Quad: 0.14
11.	Primary definition	Logistic	Primary	None	MLE	.242 (.212, .273)	.132 (.111, .157)	–.22 ± .22 (-.74, .31)	0.84

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.H-9. Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroiditis (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.241 ± .012 (.212, .269)	.135 ± .011 (.110, .161)	–.038 ± .034 (–.113, .048)	0.86
13.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.245 ± .013 (.213, .277)	.134 ± .012 (.105, .162)	–.042 ± .064 (–.191, .116)	0.74
14.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.238 ± .012 (.209, .267)	.133 ± .010 (.108, .157)	–.025 ± .027 (< –.057, .047)	0.81
15.	Primary definition	Linear	Alt. #1	None	MLE	.238 ± .012 (.210, .267)	.131 ± .010 (.107, .155)	-.016 ± .027 (<-.057, .055)	0.72
16.	Primary definition	Linear	Alt. #2	None	MLE	.240 ± .012 (.212, .268)	.134 ± .010 (.110, .158)	-.030 ± .027 (<-.062, .041)	0.85
17.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.234 ± .011 (.208, .261)	.135 ± .009 (.113, .157)	-.023 ± .026 (<-.057, .046)	0.80
18.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.235 ± .011 (.209, .261)	.135 ± .009 (.113, .158)	-.027 ± .026 (<-.057, >.041)	0.84

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

H.2.b. Alternative Definitions for Diagnosis of Autoimmune (Hashimoto's) Thyroiditis

Two alternative definitions for cases of autoimmune thyroiditis were considered. The first alternative added three participants with diagnoses based on medical records without supporting documentation, for a total of 628 (585 in-area, 43 out-of-area) cases. These three cases had estimated doses of 396, 107, and 77 mGy.

The second alternative added a single case based on a report from the participant or his/her CATI respondent, bringing the total to 629 (586 in-area, 43 out-of-area) cases. This case had an estimated dose of 8 mGy.

As shown in rows 4 and 5 of Table IX.H-9, the parameter estimates for the linear dose-response model for these alternative definitions were essentially identical to those obtained in the primary analysis (row 1). In particular there was no evidence for either alternative definition that the cumulative incidence of autoimmune thyroiditis increased with increasing dose.

H.2.b.1. Additional Outcomes Related to Assay for Antithyroid Immune Response

The HTDS diagnoses of autoimmune thyroiditis in the analyses described above were based on the AMA or anti-TPO values that were obtained as part of the participants' HTDS examinations. Since anti-TG measurements were also available, additional analyses were performed to assess the impact of incorporating anti-TG into the diagnostic criterion. Two additional diagnostic criteria were considered. The first required a positive AMA/anti-TPO, a positive anti-TG, or both, or medical records with supporting documentation, and increased the number of cases to 779. As shown in row 6 of Table IX.H-9, the estimated slope of the dose-response for this outcome was less than zero (–0.039 per Gy) with Bonferroni-adjusted 95% confidence interval ranging from less than –0.071 to 0.036 per Gy, providing no evidence that cumulative incidence increased with increasing dose ($p = 0.90$).

The second additional criterion required only a positive anti-TG or medical records with supporting documentation, resulting in a total of 507 cases. As shown in row 7 of Table IX.H-9, the estimated slope of the dose-response for this outcome was less than zero (–0.032 per Gy) with Bonferroni-adjusted 95% confidence interval ranging from less than –0.045 to 0.030 per Gy, providing no evidence that cumulative incidence increased with increasing dose ($p = 0.90$).

H.2.b.2. Additional Outcomes Related to Autoimmune (Hashimoto's) Thyroiditis and Hypothyroidism

Further analyses were made to examine the dose-responses for diagnoses of autoimmune thyroiditis with hypothyroidism. The sex-stratified linear model [1] was fit using the primary criteria for defining cases with both autoimmune thyroiditis and hypothyroidism (HTDS examination or medical record with supporting documentation). Two definitions of the outcome, varying in characteristics of hypothyroidism allowed, were considered (see section IX.H.1.b above). As shown in rows 8 and 9 of Table IX.H-9 above, for both definitions the estimated slope of the sex-stratified linear dose-response model was not significantly greater than zero ($p = 0.50$ and 0.48).

H.2.c. Alternative Dose-Response Functions

As shown in row 10 of Table IX.H-9, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.050 with Bonferroni-adjusted 95% confidence interval ranging from –0.035 to 0.134. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.14$).

In the analysis of autoimmune thyroiditis based on the HTDS examination or medical records with supporting documentation, i.e., the primary criterion for defining cases with autoimmune thyroiditis, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –0.22 with Bonferroni-adjusted 95% confidence interval ranging from –0.74 to 0.31 (Table IX.H-9, row 11). Thus there was no evidence from the logistic regression model that cumulative incidence of autoimmune thyroiditis increased with increasing dose ($p = 0.84$).

H.2.d. Effect of Excluding Participants in High Dose Categories

When participants with the highest doses were excluded, there was still no evidence that the cumulative incidence of autoimmune thyroiditis increased with increasing dose, as shown in rows 12 and 13 of Table IX.H-9.

H.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When Okanogan and Ferry/Stevens geostrata were excluded the estimated slope B was –0.025 per Gy, with Bonferoni-adjusted 95% confidence interval ranging from less than –0.057 to 0.047 per Gy, providing no evidence that the cumulative incidence of autoimmune thyroiditis increased with increasing dose ($p = 0.81$; row 14 of Table IX.H-9).

H.2.f. Analysis of Autoimmune (Hashimoto's) Thyroiditis in Relation to Alternative Dose Estimates

As shown in rows 15 and 16 of Table IX.H-9, there was no major change in the dose-response results when the alternative dose estimates were used, and in neither case was there evidence that the cumulative incidence increased with increasing dose ($p = 0.72$ and $p = 0.85$ for the first and second set of dose estimates, respectively).

H.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. In neither of the scoping analyses was there evidence that the cumulative incidence increased with increasing dose ($p = 0.80$ and $p = 0.84$ for the first and second scoping analyses, respectively; Table IX.H-9, rows 17 and 18).

H.2.h. Analysis of Autoimmune (Hashimoto's) Thyroiditis in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

H.2.h.1. Analysis by Geostratum

As shown in Table IX.H-10, the proportions of women with autoimmune thyroiditis (by HTDS or medical record with documentation) ranged from 21/75 (28.0%) for the Okanogan geostratum to 35/170 (20.6%) for the Walla Walla County geostratum. For men the proportion ranged from 57/358 (15.9%) to 51/501 (10.2%) for the Benton County and Pasco/Kennewick geostrata, respectively. This heterogeneity

among the nine geostrata was not considered statistically significant (p = 0.073). The percentages with autoimmune thyroiditis were somewhat higher in the Okanogan and Ferry/Stevens geostrata (26.6% for women, 14.2% for men) than in the remaining geostrata (22.8% and 13.0%), but this heterogeneity between combined geostrata was not statistically significant (p = 0.12).

Table IX.H-10. Diagnoses of Autoimmune Thyroiditis Based on the HTDS Evaluation or on Medical Records with Supporting Documentation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	43	24.0	173	24	13.9	352	67	19.0
Pasco/Kennewick	508	106	20.9	501	51	10.2	1009	157	15.6
Benton County	376	92	24.5	358	57	15.9	734	149	20.3
Franklin County	73	19	26.0	76	11	14.5	149	30	20.1
Adams County	165	35	21.2	156	23	14.7	321	58	18.1
Walla Walla (city)	133	35	26.3	131	18	13.7	264	53	20.1
Walla Walla County	170	35	20.6	164	19	11.6	334	54	16.2
Okanogan County	75	21	28.0	64	10	15.6	139	31	22.3
Ferry/Stevens Counties	68	17	25.0	70	9	12.9	138	26	18.8
Total	1747	403	23.1	1693	222	13.1	3440	625	18.2

H.2.h.2. Analysis by Dichotomous Exposure Variable

Of the 1257 participants included in these analyses, 210 (16.7%) had a diagnosis of autoimmune thyroiditis based on the HTDS examination or medical records with supporting documentation (see Table IX.H-11). These included 92/580 (15.9%) in the high exposure group and 118/677 (17.4%) in the low exposure group. The cumulative incidence of autoimmune thyroiditis was not significantly higher in the high exposure group (p = 0.86).

Table IX.H-11. Diagnoses of Autoimmune Thyroiditis Based on HTDS or Medical Record with Supporting Documentation, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	70	19.9	326	48	14.7	677	118	17.4
High	298	60	20.1	282	32	11.3	580	92	15.9
Total	649	130	20.0	608	80	13.2	1257	210	16.7

H.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of Hashimoto's thyroiditis, i.e., those based on an HTDS diagnosis or on medical records with documented diagnoses, and on the primary dose estimates. Table IX.H-12 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.H-12 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate.

Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.H-12, the regression coefficients did not differ significantly between the groups defined by any of the covariates, suggesting that none of them was a significant modifier of a radiation dose-response for Hashimoto's thyroiditis.

Table IX.H-12. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Autoimmune Thyroiditis

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	−.215 ± .220 (−.742, .313)	Not Applicable	−.223 ± .354 (−1.11, .660)	−.210 ± .282 (−.913, .494)	.98
Prenatal exposure?	1034 / 3191	−.215 ± .220 (−.742, .313)	−.255 ± .224 (−.832, .322)	−.183 ± .252 (−.849, .483)	−.491 ± .473 (−1.74, .756)	.56
1st exposure before age 180 days?	1478 / 3191	−.215 ± .220 (−.742, .313)	−.211 ± .222 (−.782, .360)	−.781 ± .395 (−1.82, .260)	.059 ± .251 (−.602, .720)	.071
Age at exam > 50?	2001 / 3191	−.215 ± .220 (−.742, .313)	−.310 ± .229 (−.900, .280)	−.659 ± .484 (−1.94, .617)	−.193 ± .261 (−.882, .496)	.38
NTS ^{131}I dose > 5.3 mGy?	1567 / 3189	−.214 ± .220 (−.741, .313)	−.222 ± .226 (−.803, .360)	−.354 ± .306 (−1.16, .454)	−.056 ± .328 (−.922, .810)	.51
History of any cancer other than thyroid?	248 / 3186	−.206 ± .220 (−.733, .320)	−.201 ± .221 (−.769, .367)	−.145 ± .234 (−.762, .472)	−.661 ± .762 (−2.67, 1.35)	.49
Expanded In-Person Interview?	1212 / 3191	−.215 ± .220 (−.742, .313)	−.273 ± .226 (−.855, .309)	−.783 ± .382 (−1.79, .226)	.015 ± .264 (−.681, .712)	.084

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.H-13 and IX.H-14 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposures as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Moreover the adjusted estimates all remained less than zero. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for autoimmune thyroiditis.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.H-13 and IX.H-14.

Table IX.H-13. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Autoimmune Thyroiditis

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
CAT scan of the upper body?	775 / 3149	−.209 ± .221 (−.738, .320)	−.211 ± .221 (−.780, .358)	−.225 ± .246 (−.874, .423)	−.149 ± .509 (−1.49, 1.19)	.89
Diagnostic x-rays of the head?	1191 / 3155	−.207 ± .222 (−.739, .325)	−.213 ± .223 (−.787, .360)	−.197 ± .274 (−.920, .526	−.245 ± .381 (−1.25, .761)	.92
Diagnostic x-rays of the neck?	966 / 3167	−.204 ± .221 (−.732, .325)	−.199 ± .222 (−.770, .373)	−.369 ± .301 (−1.16, .424)	.014 ± .318 (−.824, .852)	.38
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	−.199 ± .220 (−.725, .327)	−.198 ± .220 (−.765, .368)	.048 ± .773 (−1.99, 2.09)	−.219 ± .230 (−.827, .388)	.74
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	−.224 ± .224 (−.760, .311)	−.229 ± .224 (−.806, .348)	−.238 ± .250 (−.898, .422)	−.192 ± .503 (−1.52, 1.14)	.94
Barium enema?	825 / 3159	−.235 ± .223 (−.768, .298)	−.236 ± .223 (−.810, .337)	−.065 ± .248 (−.719, .588)	−.811 ± .498 (−2.13, .504)	.17
Upper GI?	1146 / 3177	−.233 ± .222 (−.764, .298)	−.227 ± .222 (−.798, .344)	−.156 ± .271 (−.872, .559)	−.360 ± .382 (−1.37, .648)	.66
Intravenous pyelogram?	398 / 3157	−.223 ± .222 (−.756, .309)	−.213 ± .222 (−.784, .359)	−.201 ± .234 (−.818, .415)	−.311 ± .700 (−2.16, 1.53)	.88
Fluoroscopy of the upper body?	246 / 3161	−.224 ± .221 (−.755, .306)	−.221 ± .221 (−.791, .349)	−.191 ± .228 (−.792, .409)	−.639 ± .886 (−2.98, 1.70)	.62
Nuclear scan (excluding thyroid scan)?	217 / 3162	−.185 ± .219 (−.709, .339)	−.178 ± .219 (−.742, .386)	−.155 ± .224 (−.746, .436)	−.579 ± .968 (−3.13, 1.97)	.66
History of any cancer other than thyroid?	248 / 3186	−.206 ± .220 (−.733, .320)	−.201 ± .221 (−.769, .367)	−.145 ± .234 (−.762, .472)	−.661 ± .762 (−2.67, 1.35)	.49
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	−.215 ± .220 (−.742, .313)	−.216 ± .220 (−.783, .351)	.092 ± .294 (−.684, .869)	−.554 ± .336 (−1.44, .332)	.15

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.H-14. Confounding and Effect Modification by Occupational History: Autoimmune Thyroiditis

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Any metal industry?	238 / 3191	−.215 ± .220 (−.742, .313)	−.217 ± .220 (−.785, .351)	−.144 ± .222 (−.730, .442)	−1.75 ± 1.15 (−4.78, 1.27)	.14
Any nuclear facility?	371 / 3191	−.215 ± .220 (−.742, .313)	−.226 ± .222 (−.798, .346)	−.196 ± .242 (−.835, .442)	−.377 ± .561 (−1.86, 1.10)	.77
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	−.215 ± .220 (−.742, .313)	−.210 ± .220 (−.777, .358)	−.079 ± .233 (−.693, .534)	−1.26 ± .800 (−3.37, .848)	.12
Any of the above industries or occupations?	892 / 3191	−.215 ± .220 (−.742, .313)	−.223 ± .221 (−.792, .346)	−.015 ± .255 (−.688, .658)	−.746 ± .448 (−1.93, .435)	.14

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.H-15 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.H-15. Confounding and Effect Modification by Smoking: Autoimmune Thyroiditis

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Cigarettes (unfiltered or filtered)?	1854 / 3183	−.210 ± .220 (−.736, .317)	−.214 ± .220 (−.781, .352)	−.664 ± .393 (−1.70, .373)	.009 ± .257 (−.668, .686)	.15
Any of cigarettes, cigar or pipe?	1900 / 3183	−.210 ± .220 (−.736, .317)	−.214 ± .220 (−.781, .352)	−.609 ± .394 (−1.65, .430)	−.021 ± .258 (−.701, .658)	.21

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

H.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for autoimmune thyroiditis are shown in Figure IX.H-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates.

The point estimate of the slope was greater than zero for only 13 of the 100 realizations, and the confidence interval included zero for all 100 realizations. Also shown in Figure IX.H-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for most realizations the estimated slope was less than 0.

Figure IX.H-1. Plot of Estimated Slope and 95% CI by Dose Realization: Autoimmune Thyroiditis

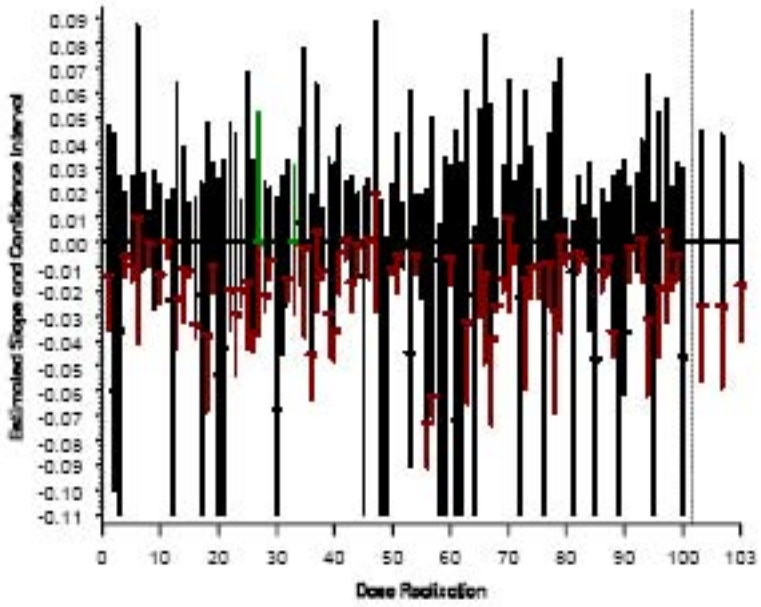
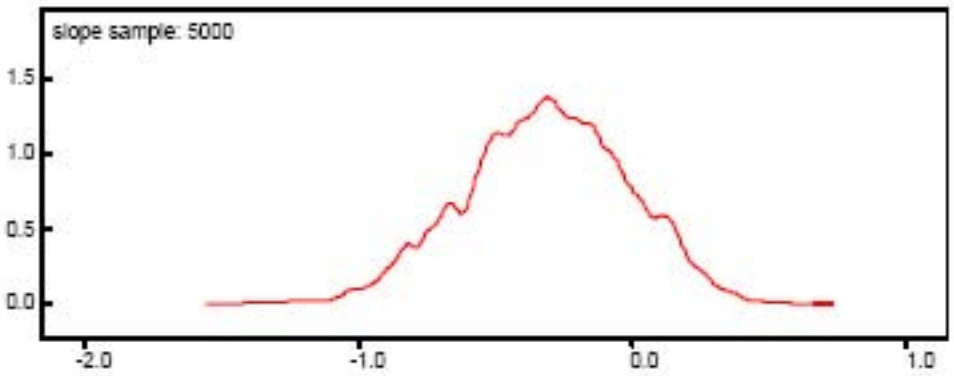


Figure IX.H-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –1.5 and 0.5. The estimate was less than or equal to 0 for 4453 of the 5000 replications, implying an empirical one-tailed p-value of 0.89. The median estimate was –0.36, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval ranging from –1.35 to 0.32. These may be compared to the estimates of –0.22 (with confidence interval ranging from –0.74 to 0.31) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of autoimmune thyroiditis increased with increasing dose.

Figure IX.H-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Autoimmune Thyroiditis



I. Graves Disease

I.1. Occurrence of Graves Disease

The primary and alternative definitions of Graves disease were as follows:

- Primary definition: HTDS evaluation or medical records with supporting documentation (34 cases)
- Alternative definition #1: HTDS evaluation or medical records with or without supporting documentation (37 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (50 cases).

Thirty-four (1.0%) living evaluable participants had a diagnosis of Graves Disease based on the HTDS evaluation or on medical records with supporting documentation (Table IX.I-1). Three (0.1%) living evaluable participants had a diagnosis of Graves Disease based on medical records without supporting documentation, and an additional thirteen (0.4%) were based on a participant or his/her CATI respondent report.

Table IX.I-1. Basis for Diagnosis of Graves Disease, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	37	2.1	13	0.8	50	1.5
▪ HTDS evaluation	5	0.3	2	0.1	7	0.2
▪ Medical records with supporting documentation	23	1.3	4	0.2	27	0.8
▪ Medical records *without* supporting documentation	3	0.2	0	--	3	0.1
▪ Participant/respondent report	6	0.3	7	0.4	13	0.4
No	1698	97.2	1673	98.8	3371	98.0
Unknown	12	0.7	7	0.4	19	0.6
Total	1747	100.0	1693	100.0	3440	100.0

Nineteen living evaluable participants were classified as "unknown" with regard to diagnosis of Graves disease. These 19 did not have medical records or participant/respondent reports of such diagnoses, and did not have an HTDS evaluation due to lack of blood draw (8) or diagnosis of hyperthyroidism with unknown etiology (potentially Graves) (11). These 19 participants were included as non-cases in analyses of the dose-response for Graves disease.

I.2. Analysis of Graves Disease Risk

I.2.a. Primary Analysis

Of the 34 living evaluable participants with a diagnosis of Graves disease based on the HTDS examination or medical records with supporting documentation, two were out-of-area participants for whom the CIDER program could not calculate dose estimates. The proportions with Graves disease are shown by sex, dose category and basis for diagnosis in Table IX.I-2.

Table IX.I-2. Diagnoses of Graves Disease by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	125	2	1.6	2	1.6	2	1.6
< 10	182	5	2.7	7	3.8	7	3.8
10-49	320	4	1.3	4	1.3	5	1.6
50-99	313	3	1.0	4	1.3	7	2.2
100-149	220	2	0.9	2	0.9	2	0.9
150-199	126	0	--	0	--	0	--
200-299	139	4	2.9	4	2.9	5	3.6
300-399	144	2	1.4	2	1.4	3	2.1
400-999	171	6	3.5	6	3.5	6	3.5
1000+	7	0	--	0	--	0	--
Total	1747	28	1.6	31	1.8	37	2.1

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	124	0	--	0	--	0	--
< 10	186	1	0.5	1	0.5	1	0.5
10-49	314	1	0.3	1	0.3	2	0.6
50-99	310	2	0.6	2	0.6	2	0.6
100-149	171	0	--	0	--	1	0.6
150-199	109	1	0.9	1	0.9	2	1.8
200-299	148	0	--	0	--	2	1.4
300-399	160	1	0.6	1	0.6	3	1.9
400-999	154	0	--	0	--	0	--
1000+	17	0	--	0	--	0	--
Total	1693	6	0.4	6	0.4	13	0.8

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.I-3 below. Based on the maximum likelihood analysis of the sex-stratified linear probability model, the estimated slope B was slightly less than zero (–0.001 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.002 to 0.024 per Gy, providing no evidence that cumulative incidence increased with increasing dose (one-tailed p=0.56; row 1 of Table IX.I-3). The corresponding estimated background rates for diagnosis of Graves disease were 0.016 with confidence interval (0.008, 0.025) for women and 0.004 with confidence interval (0, 0.009) for men.

As shown in rows 2 and 3 of Table IX.I-3, generally similar results were obtained when the model was fit by the method of least squares. The estimates of the slope were slightly but not significantly greater than zero (p = 0.26 and 0.13 for ungrouped and grouped data, respectively).

Table IX.I-3. Summary of Dose-Response Results for Diagnoses of Graves Disease

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation or medical record with documentation)	Linear	Primary	None	MLE	.016 ± .004 (.008, .025)	.004 ± .002 (0*, .009)	–.001 ± .009 (< –.002, .024)	0.56
2.	Primary definition	Linear	Primary	None	LSU	.015 ± .003 (.008, .022)	.003 ± .003 (0*, .010)	.005 ± .008 (–.014, .024)	0.26
3.	Primary definition	Linear	Primary	None	LSG	.014 ± .003 (.007, .021)	.002 ± .003 (0*, .009)	.010 ± .009 (–.012, .032)	0.13
4.	Alternative def. #1 (HTDS or medical record with or without documentation)	Linear	Primary	None	MLE	.018 ± .004 (.009, .027)	.004 ± .002 (0*, .009)	–.002 ± .009 (NE, .020)	0.64
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.021 ± .004 (.011, .032)	.008 ± .003 (.001, .016)	.001 ± .013 (< –.004, .034)	0.48

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.I-3. Summary of Dose-Response Results for Diagnoses of Graves Disease (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Primary definition	LQ	Primary	None	LSU	.014 ± .003 (.007, .022)	.002 ± .003 (0*, .010)	Lin: .014 ± .013 (–.020, .047) Quad: –.007 ± .009 (–.029, .015)	Quad: 0.43
7.	Primary definition	Logistic	Primary	None	MLE	.015 (.008, .026)	.004 (.001, .010)	.42 ± .65 (-1.13, 1.96)	0.28
8.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.016 ± .004 (.007, .025)	.004 ± .002 (0*, .008)	.001 ± .009 (<-.005, .029)	0.44
9.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.014 ± .003 (.006, .022)	.004 ± .002 (0*, .010)	.0005 ± .012 (–.023, .037)	0.48
10.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.015 ± .004 (.006, .024)	.002 ± .002 (0*, .006)	.003 ± .008 (< –.001, .027)	0.36
11.	Primary definition	Linear	Alt. #1	None	MLE	.016 ± .003 (.008, .025)	.004 ± .002 (0*, .009)	–.002 ± .008 (NE, .015)	0.70

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.I-3. Summary of Dose-Response Results for Diagnoses of Graves Disease

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #2	None	MLE	.015 ± .004 (.007, .024)	.003 ± .002 (0*, .008)	.003 ± .008 (< –.002, .026)	0.34
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.016 ± .003 (.008, .024)	.004 ± .002 (0*, .008)	.000 ± .008 (< –.002, >.025)	0.50
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.016 ± .003 (.008, .024)	.004 ± .002 (0*, .008)	–.0003 ± .008 (< –.002, >.024)	0.51

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

I.2.b. Alternative Definitions for Diagnosis of Graves Disease

Two alternative definitions for cases of Graves disease were considered. The first alternative added three cases with diagnoses based on medical records without supporting documentation, for a total of 37 cases. The second alternative criterion for defining cases of Graves disease added another 13 cases based solely on a report from the participant or his/her CATI respondent, for a total of 50 cases. As shown in rows 4 and 5 of Table IX.I-3 above, for neither of these alternative definitions was there any evidence that the cumulative incidence of Graves disease increased significantly with increasing dose ($p = 0.64$ and $p = 0.48$ for the first and second alternative criteria respectively).

I.2.c. Alternative Dose-Response Functions

As shown in row 6 of Table IX.I-3, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was –0.007 with Bonferroni-adjusted 95% confidence interval ranging from –0.029 to 0.015. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.43$).

In the analysis of Graves disease based on the HTDS examination or medical records with supporting documentation, i.e., the primary definition of Graves disease, the regression parameter for the effect of dose in the sex-stratified logistic regression model was estimated as 0.42 with Bonferroni-adjusted 95% confidence interval ranging from –1.13 to 1.96 (row 7 of Table IX.I-3). Thus the cumulative incidence of Graves disease did not increase significantly with increasing dose ($p = 0.28$).

I.2.d. Effect of Excluding Participants in High Dose Categories

As shown in row 8 of Table IX.I-3, when participants with estimated dose > 1000 mGy were excluded, the estimated slope B was not significantly greater than zero (0.001 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than –0.005 to 0.029 per Gy; $p = 0.44$). Similar results were obtained when participants with estimated dose > 400 mGy were excluded (Table IX.I-3, row 9).

I.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

As shown in row 10 of Table IX.I-3, when Okanogan and Ferry/Stevens geostrata were excluded, the estimated slope B was not significantly greater than zero (0.003 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from less than –0.001 to 0.027 per Gy; $p = 0.36$).

I.2.f. Analysis of Graves Disease in Relation to Alternative Dose Estimates

For neither set of alternative dose estimates did the cumulative incidence increase significantly with increasing dose ($p = 0.70$ and $p = 0.34$ for the first and second set of alternative dose estimates, respectively; Table IX.I-3, rows 11 and 12).

I.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 13 and 14 of Table IX.I-3, in neither scoping analysis was there any evidence that the cumulative incidence of Graves Disease

increased with increasing dose (p = 0.50 and p = 0.51 for the first and second scoping analyses, respectively).

I.2.h. Analysis of Graves Disease in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

I.2.h.1. Analysis by Geostratum

There were too few participants (34) with diagnoses of Graves disease (from the HTDS examination or medical records with documentation) for a definitive conclusion regarding heterogeneity among the geostrata (see Table IX.I-4). The absence of significant heterogeneity (p = 0.43) was not strong evidence against the possibility that the cumulative incidence of Graves disease might vary among geostrata. The percentages with Graves disease were somewhat higher in the Okanogan and Ferry/Stevens geostrata (2.8% for women, 1.5% for men) than in the remaining geostrata (1.5% and 0.3%), but this heterogeneity between combined geostrata was also not statistically significant (p = 0.13).

Table IX.I-4. Diagnoses of Graves Disease Based on the HTDS Evaluation or on Medical Records with Supporting Documentation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	3	1.7	173	0	--	352	3	0.9
Pasco/Kennewick	508	10	2.0	501	1	0.2	1009	11	1.1
Benton County	376	5	1.3	358	1	0.3	734	6	0.8
Franklin County	73	1	1.4	76	1	1.3	149	2	1.3
Adams County	165	3	1.8	156	1	0.6	321	4	1.2
Walla Walla (city)	133	1	0.8	131	0	--	264	1	0.4
Walla Walla County	170	1	0.6	164	0	--	334	1	0.3
Okanogan County	75	2	2.7	64	1	1.6	139	3	2.2
Ferry/Stevens Counties	68	2	2.9	70	1	1.4	138	3	2.2
Total	1747	28	1.6	1693	6	0.4	3440	34	1.0

I.2.h.2. Analysis by Dichotomous Exposure Variable

Only 13 (1.0%) of the 1257 participants included in these analyses had a diagnosis of Graves disease based on the HTDS examination or medical records with supporting documentation (see Table IX.I-5). These included 7/580 (1.2%) in the high exposure group and 6/677 (0.9%) in the low exposure group. The cumulative incidence of Graves disease was not significantly greater in the high exposure group (p = 0.24).

Table IX.I-5. Diagnoses of Graves Disease based on HTDS or Medical Record with Supporting Documentation, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	5	1.4	326	1	0.3	677	6	0.9
High	298	6	2.0	282	1	0.4	580	7	1.2
Total	649	11	1.7	608	2	0.3	1257	13	1.0

I.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of Graves Disease; those based on an HTDS diagnosis or on medical records with documented diagnoses, and on the primary dose estimates. Table IX.I-6 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.I-6 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate. Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.I-6, the regression coefficients did not differ significantly between the groups defined by any of the covariates, suggesting that none of them was a significant modifier of a radiation dose-response for Graves disease.

Table IX.I-6. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Graves Disease

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	.415 ± .646 (–1.13, 1.96)	Not Applicable	–1.78 ± 2.83 (–8.85, 5.29)	.635 ± .622 (–.918, 2.19)	.32
Prenatal exposure?	1034 / 3191	.415 ± .646 (–1.13, 1.96)	.370 ± .659 (–1.33, 2.07)	.440 ± .704 (–1.42, 2.30)	.038 ± 1.67 (–4.37, 4.44)	.82
1st exposure before age 180 days?	1478 / 3191	.415 ± .646 (–1.13, 1.96)	.393 ± .643 (–1.26, 2.05)	2.03 ± 1.01 (–.633, 4.69)	-.771 ± 1.32 (–4.26, 2.72)	.071
Age at exam > 50?	2001 / 3191	.415 ± .646 (–1.13, 1.96)	.493 ± .625 (–1.12, 2.10)	.267 ± 1.11 (–2.66, 3.20)	.628 ± .765 (–1.39, 2.64)	.78
NTS ^{131}I dose > 5.3 mGy?	1567 / 3189	.415 ± .646 (–1.13, 1.96)	.319 ± .691 (–1.46, 2.10)	.770 ± .679 (–1.02, 2.56)	–2.08 ± 2.52 (–8.72, 4.56)	.19
History of any cancer other than thyroid?	248 / 3186	.415 ± .646 (–1.13, 1.96)	.508 ± .682 (–1.25, 2.26)	.508 ± .682 (–1.29, 2.31)	0.0 ± 1115 (–2943, 2943)	1.0
Expanded In-Person Interview?	1212 / 3191	.415 ± .646 (–1.13, 1.96)	.499 ± .651 (–1.18, 2.18)	1.40 ± .992 (–1.22, 4.01)	-.275 ± 1.27 (–3.64, 3.09)	.26

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.I-7 and IX.I-8 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposures as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Thus there was no evidence that omitting these factors introduces any important bias in the dose-response results for Graves Disease.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.I-7 and IX.I-8, with the possible exception of history of diagnostic x-rays of the chest or upper back, including mammograms (Table IX.I-7). However the regression parameter for the 352 participants without such histories is extremely negative, –275, with an extremely wide confidence interval (–817, 267), since only two participants in this group had diagnoses of Graves disease (both women with doses less than 10 mGy). Therefore the p-value of 0.002 for effect modification must be interpreted cautiously. It is noteworthy that the regression parameter for the larger group of participants with histories of chest or upper body diagnostic x-rays or mammograms (0.534 with confidence interval ranging from –1.07 to 2.14) differs little from the overall estimate of 0.414 with confidence interval (–1.13, 1.96).

Table IX.I-7. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Graves Disease

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
CAT scan of the upper body?	775 / 3149	.423 ± .650 (–1.13, 1.98)	.433 ± .654 (–1.25, 2.12)	.421 ± .716 (–1.47, 2.31)	.500 ± 1.66 (–3.88, 4.88)	.97
Diagnostic x-rays of the head?	1191 / 3155	.423 ± .642 (–1.11, 1.96)	.421 ± .635 (–1.22, 2.06)	.246 ± .852 (–2.00, 2.50)	.721 ± .973 (–1.84, 3.29)	.72
Diagnostic x-rays of the neck?	966 / 3167	.376 ± .670 (–1.23, 1.98)	.329 ± .669 (–1.39, 2.05)	.212 ± 1.14 (–2.79, 3.21)	.392 ± .804 (–1.73, 2.51)	.90
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	.414 ± .646 (–1.13, 1.96)	.439 ± .641 (–1.21, 2.09)	–275 ± 205 (–817, 267)	.534 ± .608 (–1.07, 2.14)	.002
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	.427 ± .642 (–1.11, 1.96)	.412 ± .644 (–1.25, 2.07)	.362 ± .714 (–1.52, 2.24)	.669 ± 1.48 (–3.23, 4.57)	.86
Barium enema?	825 / 3159	.368 ± .673 (–1.24, 1.98)	.375 ± .675 (–1.36, 2.11)	.685 ± .699 (–1.16, 2.53)	–.650 ± 1.69 (–5.10, 3.80)	.42
Upper GI?	1146 / 3177	.417 ± .645 (–1.13, 1.96)	.409 ± .647 (–1.26, 2.08)	.536 ± .744 (–1.43, 2.50)	.120 ± 1.25 (–3.17, 3.41)	.77
Intravenous pyelogram?	398 / 3157	.376 ± .670 (–1.23, 1.98)	.382 ± .664 (–1.33, 2.09)	.386 ± .681 (–1.41, 2.18)	.318 ± 2.87 (–7.26, 7.90)	.98
Fluoroscopy of the upper body?	246 / 3161	.381 ± .667 (–1.22, 1.98)	.393 ± .667 (–1.33, 2.11)	.336 ± .713 (–1.54, 2.22)	1.13 ± 2.35 (–5.08, 7.34)	.76
Nuclear scan (excluding thyroid scan)?	217 / 3162	.418 ± .643 (–1.12, 1.96)	.417 ± .640 (–1.23, 2.07)	.382 ± .659 (–1.36, 2.12)	2.11 ± 4.02 (–8.48, 12.7)	.69
History of any cancer other than thyroid cancer?	248 / 3186	.415 ± .646 (–1.13, 1.96)	.508 ± .682 (–1.25, 2.26)	.508 ± .682 (–1.29, 2.31)	0.0 ± 1115 (–2943, 2943)	1.0
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	.415 ± .646 (–1.13, 1.96)	.403 ± .654 (–1.28, 2.09)	.271 ± .914 (–2.14, 2.68)	.558 ± .91 (–1.83, 2.95)	.82

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.I-8. Confounding and Effect Modification by Occupational History: Graves Disease

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Any metal industry?	238 / 3191	.415 ± .646 (–1.13, 1.96)	.423 ± .643 (–1.23, 2.08)	.329 ± .687 (–1.48, 2.14)	3.33 ± 3.19 (–5.09, 11.8)	.40
Any nuclear facility?	371 / 3191	.415 ± .646 (–1.13, 1.96)	.390 ± .674 (–1.35, 2.13)	.399 ± .699 (–1.44, 2.24)	.292 ± 2.40 (–6.04, 6.63)	.97
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	.415 ± .646 (–1.13, 1.96)	.434 ± .631 (–1.19, 2.06)	.242 ± .804 (–1.88, 2.36)	.801 ± .93 (–1.64, 3.24)	.66
Any of the above industries or occupations?	892 / 3191	.415 ± .646 (–1.13, 1.96)	.402 ± .649 (–1.27, 2.07)	.361 ± .811 (–1.78, 2.50)	.480 ± 1.07 (–2.35, 3.31)	.93

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.I-9 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.I-9. Confounding and Effect Modification by Smoking: Graves Disease

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficent (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Cigarettes (unfiltered or filtered)?	1854 / 3183	.407 ± .658 (–1.17, 1.98)	.439 ± .666 (–1.28, 2.15)	.665 ± 1.05 (–2.11, 3.44)	.300 ± .90 (–2.08, 2.68)	.79
Any of cigarettes, cigar or pipe?	1900 / 3183	.407 ± .658 (–1.17, 1.98)	.441 ± .666 (–1.28, 2.16)	.663 ± 1.052 (–2.11, 3.44)	.303 ± .90 (–2.08, 2.69)	.80

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

I.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for Graves disease are shown in Figure IX.I-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. The point estimate of the slope was greater than 0 for 48 of the 100 realizations, and the confidence interval included 0 for all 100 realizations. Also shown in Figure IX.I-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for about half of the realizations the estimated slope was less than 0.

Figure IX.I-1. Plot of estimated Slope and 95% CI by Dose Realization: Graves Disease

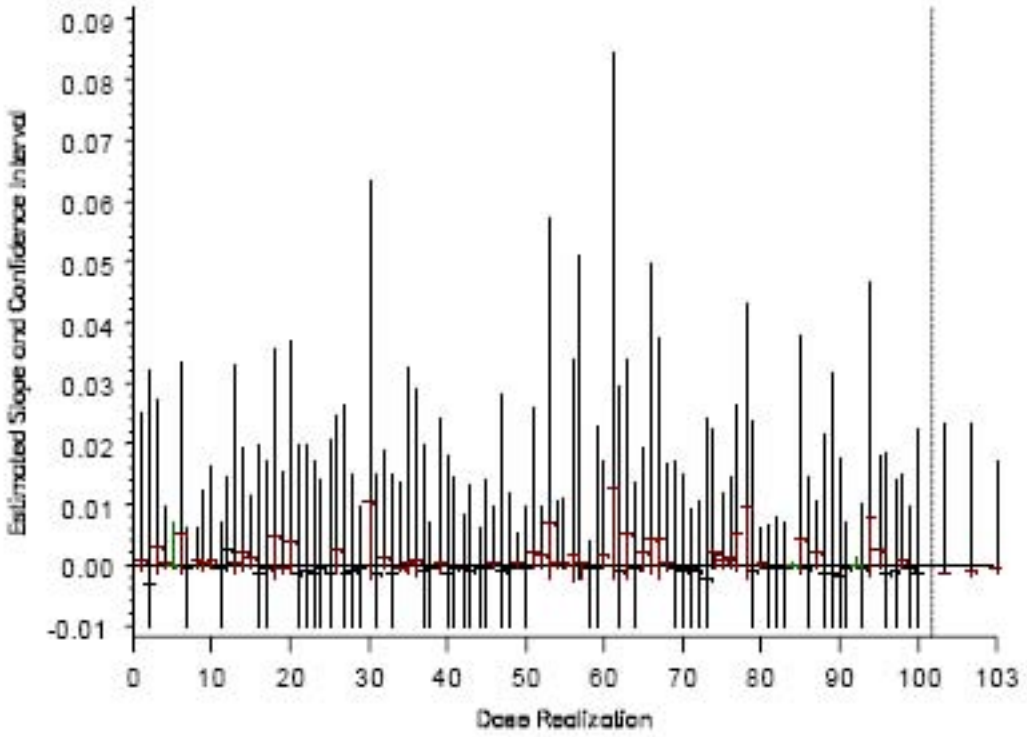
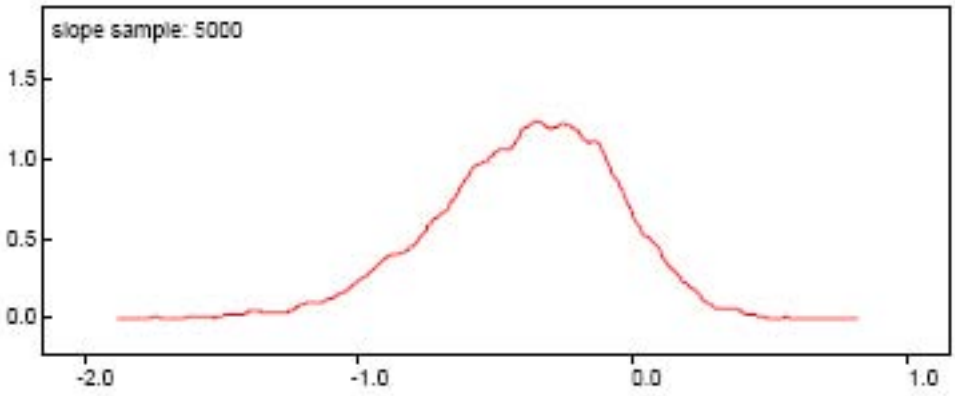


Figure IX.I-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –1.5 and 0.5. The estimate was less than or equal to 0 for 2068 of the 5000 replications, implying an empirical one-tailed p-value of 0.41. The median estimate was 0.21, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –3.21 and 1.87. These may be compared to the estimate of 0.42 with confidence interval (–1.13, 1.96) obtained using the median dose estimate without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of Graves disease increased with increasing dose.

Figure IX.I-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Graves Disease



J. Autoimmune Thyroid Disease

J.1. Occurrence of Autoimmune Thyroid Disease

Autoimmune thyroid disease was defined by diagnosis of autoimmune (Hashimoto's) thyroiditis or Graves disease. The primary and alternative definitions of autoimmune thyroid disease were as follows:

- Primary definition: Diagnosis of autoimmune thyroiditis or Graves disease based on HTDS evaluation or medical records with supporting documentation (659 cases)
- Alternative definition #1: HTDS evaluation or medical records with or without supporting documentation (663 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (674 cases).

Of the 3440 living evaluable participants, 659 (19.2%) had a diagnosis of autoimmune thyroid disease based on the HTDS evaluation or medical records with supporting documentation (Table IX.J-1). These included 625 with autoimmune (Hashimoto's) thyroiditis (see section IX.H) and 34 others with diagnoses of Graves disease (see section IX.I). An additional 4 (0.1%) living evaluable participants had a diagnosis of autoimmune thyroid disease based on medical records without supporting documentation (three with autoimmune thyroiditis, one with Graves disease). Eleven other participants (0.3%) were based on a report by the participant or his/her CATI respondent (one with autoimmune thyroiditis, 10 with Graves disease).

Table IX.J-1. Basis for Diagnosis of Autoimmune Thyroid Disease, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	442	25.3	232	13.7	674	19.6
▪ HTDS Evaluation	421	24.1	226	13.3	647	18.8
▪ Medical Records with supporting documentation	10	0.6	2	0.1	12	0.3
▪ Medical Records *without* supporting documentation	4	0.2	0	--	4	0.1
▪ Participant/respondent report	7	0.4	4	0.2	11	0.3
No	1296	74.2	1454	85.9	2750	79.9
Unknown	9	0.5	7	0.4	16	0.5
Total	1747	100.0	1693	100.0	3440	100.0

Sixteen living evaluable participants were classified as "unknown" with regard to diagnosis of autoimmune thyroid disease. These sixteen did not have medical record or participant/respondent reports of such diagnoses, and did not have an HTDS evaluation due to lack of a blood draw (N=8), insufficient amount of blood drawn to obtain the antibody level (N=1), and a diagnosis of hyperthyroidism with an uncertain etiology (potentially Graves) (N=7). These sixteen participants were included as non-cases in analyses of the dose-response for autoimmune thyroid disease.

J.2. Analysis of Autoimmune Thyroid Disease Risk

J.2.a. Primary Analysis

Of the 659 living evaluable participants with a diagnosis of autoimmune thyroid disease based on the HTDS examination or medical records with supporting documentation, 45 were out-of-area participants. The proportions with autoimmune thyroid disease are shown by sex, dose category and basis for diagnosis in Table IX.J-2.

Table IX.J-2. Diagnoses of Autoimmune Thyroid Disease by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	125	24	19.2	24	19.2	24	19.2
< 10	182	49	26.9	49	26.9	50	27.5
10-49	320	75	23.4	75	23.4	76	23.8
50-99	313	84	26.8	86	27.5	89	28.4
100-149	220	55	25.0	56	25.5	56	25.5
150-199	126	36	28.6	36	28.6	36	28.6
200-299	139	33	23.7	33	23.7	34	24.5
300-399	144	35	24.3	36	25.0	37	25.7
400-999	171	38	22.2	38	22.2	38	22.2
1000+	7	2	28.6	2	28.6	2	28.6
Total	1747	431	24.7	435	24.9	442	25.3

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	124	21	16.9	21	16.9	21	16.9
< 10	186	27	14.5	27	14.5	27	14.5
10-49	314	41	13.1	41	13.1	41	13.1
50-99	310	49	15.8	49	15.8	49	15.8
100-149	171	17	9.9	17	9.9	18	10.5
150-199	109	13	11.9	13	11.9	14	12.8
200-299	148	18	12.2	18	12.2	20	13.5
300-399	160	21	13.1	21	13.1	21	13.1
400-999	154	20	13.0	20	13.0	20	13.0
1000+	17	1	5.9	1	5.9	1	5.9
Total	1693	228	13.5	228	13.5	232	13.7

Since nearly all of the cases of autoimmune thyroid disease were in fact autoimmune thyroiditis, it was to be expected that dose-response results for these two disease outcomes would be quite similar. Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.J-3 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was slightly less than zero (–0.024 per Gy; row 1 of Table IX.J-3) with Bonferroni-adjusted 95% confidence interval ranging from less than –0.058 to 0.048, providing no evidence that cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.80$). The corresponding estimated background rates for diagnosis of autoimmune thyroid disease were 0.255 with confidence interval (0.227, 0.283) for women and 0.136 with confidence interval (0.112, 0.160) for men. Very similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data (Table IX.J-3, rows 2 and 3).

Table IX.J-3. Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroid Disease

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation or medical record with documentation)	Linear	Primary	None	MLE	.255 ± .012 (.227, .283)	.136 ± .010 (.112, .160)	–.024 ± .027 (<-.058, .048)	0.80
2.	Primary definition	Linear	Primary	None	LSU	.255 ± .011 (.229, .282)	.136 ± .011 (.109, .163)	–.024 ± .031 (–.098, .049)	0.79
3.	Primary definition	Linear	Primary	None	LSG	.257 ± .011 (.230, .285)	.139 ± .012 (.111, .167)	–.038 ± .036 (–.123, .047)	0.86
4.	Alternative def. #1 (HTDS or medical record with or without documentation)	Linear	Primary	None	MLE	.258 ± .012 (.229, .286)	.136 ± .010 (.112, .160)	–.024 ± .027 (<-.058, .048)	0.80
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.262 ± .012 (.234, .291)	.139 ± .010 (.115, .163)	–.026 ± .028 (-<.059, .047)	0.81

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.J-3 Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroid Disease (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Primary definition	LQ	Primary	None	LSU	.261 ± .012 (.231, .290)	.142 ± .012 (.112, .172)	Lin: –.076 ± .052 (–.207, .054) Quad: .043 ± .035 (–.044, .129)	Quad: 0.22
7.	Primary definition	Logistic	Primary	None	MLE	.256 (.227, .288)	.135 (.114, .160)	–.17 ± .21 (-.68, .34)	0.79
8.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.256 ± .012 (.227, .285)	.138 ±.011 (.113, .163)	-.031 ± .035 (<-.109, .057)	0.81
9.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.259 ± .014 (.226, .292)	.138 ± .012 (.109, .166)	-.041 ± .065 (-.191, .119)	0.74
10.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.252 ± .012 (.223, .282)	.134 ± .010 (.110, .159)	-.020 ± .028 (<-.058, .054)	0.76
11.	Primary definition	Linear	Alt. #1	None	MLE	.255 ± .012 (.226, .284)	.136 ± .010 (.112, .160)	-.021 ± .028 (<-.058, .051)	0.76

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.J-3. Summary of Dose-Response Results for Diagnoses of Autoimmune Thyroid Disease (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #2	None	MLE	.255 ± .012 (.226, .284)	.136 ± .010 (.112, .161)	-.023 ± .029 (<-.064, .050)	0.78
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.250 ± .011 (.223, .277)	.138 ± .009 (.115, .161)	-.021 ± .027 (<-.059, >.051)	0.77
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.251 ± .011 (.224, .278)	.139 ± .009 (.116, .161)	-.024 ± .027 (<-.059, >.046)	0.81

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

J.2.b. Alternative Definitions for Diagnosis of Autoimmune Thyroid Disease

Two alternative definitions for cases of autoimmune thyroid disease were considered. The first alternative added four cases with diagnoses based on medical records without supporting documentation, for a total of 663 cases. The second added another 11 cases based solely on a report from the participant or his/her CATI respondent, for a total of 674 cases. As shown in rows 4 and 5 of Table IX.J-3 above, the parameter estimates for the linear dose-response model were essentially identical to those obtained in the primary analysis. In particular there was no evidence in either the primary or alternative analyses that the cumulative incidence of autoimmune thyroid disease increased with increasing dose.

J.2.c. Alternative Dose-Response Functions

As shown in row 6 of Table IX.J-3, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.043 with Bonferroni-adjusted 95% confidence interval ranging from –0.044 to 0.129. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.22$).

In the analysis of autoimmune thyroid disease based on the HTDS examination or medical records with supporting documentation, i.e., the primary criterion for defining cases with autoimmune thyroid disease, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –0.17 with Bonferroni-adjusted 95% confidence interval ranging from –0.68 to 0.34 (Table IX.J-3, row 7). Thus there was no evidence from the logistic regression model that cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.79$).

J.2.d. Effect of Excluding Participants in High Dose Categories

The results were essentially unchanged if participants in the high dose categories were excluded. As shown in row 8 of Table IX.J-3, if participants with estimated doses over 1000 mGy were excluded, the estimated slope of the sex-stratified linear dose-response model was less than zero (–0.031 per Gy) with Bonferroni-adjusted 95% confidence interval ranging from less than –0.109 to 0.057 per Gy. Thus there was no evidence that the cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.81$). Similar results were obtained if participants with estimated doses exceeding 400 mGy were excluded ($p = 0.74$; Table IX.J-3, row 9).

J.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

As shown in row 10 of Table IX.J-3, if the Okanogan and Ferry/Stevens geostrata were excluded, the estimated slope increased slightly from –0.024 to –0.020 per Gy, but there was no evidence that the cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.76$).

J.2.f. Analysis of Autoimmune Thyroid Disease in Relation to Alternative Dose Estimates

As shown in rows 11 and 12 of Table IX.J-3, for neither set of alternative dose estimates was there any evidence that the cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.76$ and $p = 0.78$ for the first and second dose set estimates, respectively).

J.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As shown in rows 13 and 14 of Table IX.J-3 above, for neither of the scoping analyses was there any evidence that the cumulative incidence of autoimmune thyroid disease increased with increasing dose ($p = 0.77$ and $p = 0.81$ for the first and second scoping analyses, respectively).

J.2.h. Analysis of Autoimmune Thyroid Disease in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

J.2.h.1. Analysis by Geostratum

As shown in Table IX.J-4, among the entire 3440 living evaluable participants, the proportions with autoimmune thyroid disease ranged from 23/75 (30.7% in the Okanogan County geostratum) to 36/170 (21.2%, Walla Walla County) for women, and from 11/64 (17.2%, Okanogan County) to 52/501 (10.4%, Pasco/Kennewick) for men ($p = 0.083$ for heterogeneity among the nine geostrata). In particular the percentages with autoimmune thyroid disease were somewhat higher in the Okanogan and Ferry/Stevens geostrata (29.4% for women, 15.7% for men) than in the remaining geostrata (24.3% and 13.3%, respectively; $p = 0.048$). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.J-4. Diagnoses of Autoimmune Thyroid Disease based on the HTDS Evaluation or on Medical Records with Supporting Documentation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	46	25.7	173	24	13.9	352	70	19.9
Pasco/Kennewick	508	116	22.8	501	52	10.4	1009	168	16.7
Benton County	376	97	25.8	358	58	16.2	734	155	21.1
Franklin County	73	20	27.4	76	12	15.8	149	32	21.5
Adams County	165	38	23.0	156	24	15.4	321	62	19.3
Walla Walla (city)	133	36	27.1	131	18	13.7	264	54	20.5
Walla Walla County	170	36	21.2	164	19	11.6	334	55	16.5
Okanogan County	75	23	30.7	64	11	17.2	139	34	24.5
Ferry/Stevens Counties	68	19	27.9	70	10	14.3	138	29	21.0
Total	1747	431	24.7	1693	228	13.5	3440	659	19.2

J.2.h.2. Analysis by Dichotomous Exposure Variable

A total of 223 (17.7%) of the 1257 participants included in these analyses had a diagnosis of autoimmune thyroid disease based on the HTDS examination or medical records with supporting documentation (see Table IX.J-5). These included 99/580 (17.1%) in the high exposure group and 124/677 (18.3%) in the low exposure group. The cumulative incidence of autoimmune thyroid disease was not significantly higher in the high exposure group ($p = 0.80$).

Table IX.J-5. Diagnoses of Autoimmune Thyroid Disease based on the HTDS evaluation or on Medical Records with Supporting Documentation, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	75	21.4	326	49	15.0	677	124	18.3
High	298	66	22.1	282	33	11.7	580	99	17.1
Total	649	141	21.7	608	82	13.5	1257	223	17.7

J.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of autoimmune thyroid disease, i.e., those based on an HTDS diagnosis or on medical records with documented diagnoses, and on the primary dose estimates. Table IX.J-6 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid disease, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.J-6 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate. Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.J-6, the regression coefficients did not differ significantly between the groups defined by any of the covariates, suggesting that none of them was a significant modifier of a radiation dose-response for autoimmune thyroid disease.

Table IX.J-6. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Autoimmune Thyroid Disease

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	−.170 ± .213 (−.680, .341)	Not Applicable	−.259 ± .353 (−1.14, .622)	−.116 ± .268 (−.785, .553)	.74
Prenatal exposure?	1034 / 3191	−.170 ± .213 (−.680, .341)	−.211 ± .217 (−.770, .347)	−.134 ± .244 (−.777, .509)	−.467 ± .461 (−1.68, .748)	.52
1st exposure before age 180 days?	1478 / 3191	−.170 ± .213 (−.680, .341)	−.167 ± .214 (−.719, .385)	−.550 ± .377 (−1.55, .445)	.019 ± .249 (−.638, .676)	.21
Age at exam > 50?	2001 / 3191	−.170 ± .213 (−.680, .341)	−.250 ± .221 (−.818, .319)	−.574 ± .457 (−1.78, .633)	−.136 ± .253 (−.805, .532)	.39
NTS ^{131}I dose > 5.3 mGy?	1567 / 3189	−.169 ± .213 (−.679, .342)	−.185 ± .219 (−.749, .379)	−.239 ± .291 (−1.01, .529)	−.114 ± .330 (−.984, .756)	.78
History of any cancer other than thyroid?	248 / 3186	−.161 ± .213 (−.671, .348)	−.154 ± .214 (−.704, .397)	−.094 ± .227 (−.692, .504)	−.661 ± .762 (−2.67, 1.35)	
Expanded In-Person Interview?	1212 / 3191	−.170 ± .213 (−.680, .341)	−.218 ± .218 (−.781, .345)	−.595 ± .364 (−1.55, .365)	.002 ± .261 (−.688, .691)	.18

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.J-7 and IX.J-8 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposures as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Moreover the adjusted estimates all remained less than zero. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for autoimmune disease.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.J-7 and IX.J-8.

Table IX.J-7. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Autoimmune Thyroid Disease

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
CAT scan of the upper body?	775 / 3149	−.164 ± .214 (−.676, .348)	−.166 ± .214 (−.717, .385)	−.181 ± .238 (−.808, .447)	−.100± .495 (−1.41, 1.21)	.88
Diagnostic x-rays of the head?	1191 / 3155	−.160 ± .215 (−.674, .354)	−.166 ± .215 (−.720, .388)	−.168 ± .266 (−.870, .534)	−.162 ± .366 (−1.13, .803)	.99
Diagnostic x-rays of the neck?	966 / 3167	−.164 ± .214 (−.676, .349)	−.162 ± .215 (−.715, .392)	−.343 ± .294 (−1.12, .432)	.057 ± .306 (−.749, .864)	.35
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	−.154 ± .213 (−.663, .355)	−.152 ± .213 (−.700, .397)	−.091 ± .787 (−2.17, 1.99)	−.156 ± .221 (−.740, .427)	.94
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	−.176 ± .216 (−.694, .342)	−.182 ± .216 (−.739, .376)	−.192 ± .241 (−.829, .444)	−.136 ± .489 (−1.43, 1.15)	.92
Barium enema?	825 / 3159	−.194 ± .216 (−.711, .323)	−.195 ± .216 (−.751, .361)	−.007 ± .240 (−.640, .626)	−.821 ± .485 (−2.10, .458)	.12
Upper GI?	1146 / 3177	−.186 ± .215 (−.700, .327)	−.181 ± .214 (−.733, .371)	−.101 ± .262 (−.791, .590)	−.333 ± .371 (−1.31, .646)	.61
Intravenous Pyelogram?	398 / 3157	−.182 ± .215 (−.698, .333)	−.171 ± .215 (−.725, .383)	−.159 ± .226 (−.755, .438)	−.285 ± .687 (−2.10, 1.53)	.86
Fluoroscopy of the upper body?	246 / 3161	−.183 ± .215 (−.697, .331)	−.179 ± .215 (−.731, .374)	−.157 ± .221 (−.740, .427)	−.487 ± .846 (−2.72, 1.74)	.70
Nuclear scan (excluding thyroid scan)?	217 / 3162	−.141 ± .212 (−.648, .367)	−.134 ± .212 (−.680, .412)	−.115 ± .217 (−.687, .457)	−.482 ± .947 (−2.98, 2.02)	.70
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	−.170 ± .213 (−.680, .341)	−.172 ± .213 (−.721, .377)	.111 ± .286 (−.643, .866)	−.484 ± .325 (−1.34, .372)	.17

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.J-8. Confounding and Effect Modification by Occupational History: Autoimmune Thyroid Disease

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Any metal industry?	238 / 3191	–.170 ± .213 (–.680, .341)	–.171 ± .213 (–.720, .379)	–.111 ± .216 (–.680, .458)	–1.42 ± 1.08 (–4.27, 1.43)	.21
Any nuclear facility?	371 / 3191	–.170 ± .213 (–.680, .341)	–.184 ± .215 (–.739, .371)	–.152 ± .234 (–.769, .465)	–.351 ± .550 (–1.80, 1.10)	.74
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	–.170 ± .213 (–.680, .341)	–.162 ± .213 (–.711, .387)	–.059 ± .227 (–.658, .540)	–.895 ± .710 (–2.77, .977)	.22
Any of the above industries or occupations?	892 / 3191	–.170 ± .213 (–.680, .341)	–.178 ± .214 (–.729, .373)	.014 ± .248 (–.641, .669)	–.654 ± .429 (–1.79, .477)	.16

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.J-9 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.J-9. Confounding and Effect Modification by Smoking: Autoimmune Thyroid Disease

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Cigarettes (unfiltered or filtered)?	1854 / 3183	–.167 ± .213 (–.677, .344)	–.170 ± .213 (–.719, .379)	–.563 ± .378 (–1.56, .433)	.028 ± .251 (–.634, .691)	.19
Any of cigarettes, cigar or pipe?	1900 / 3183	–.167 ± .213 (–.677, .344)	–.170 ± .213 (–.719, .379)	–.510 ± .378 (–1.51, .488)	–.001 ± .252 (–.665, .663)	.26

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

J.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for autoimmune thyroid disease are shown in Figure IX.J-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for only 16 of the 100 realizations, the confidence interval includes 0 for all 100 realizations. Also shown in Figure IX.J-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for most of the realizations the estimated slope was less than 0.

Figure IX.J-1. Plot of Estimated Slope and 95% CI by Dose Realization: Autoimmune Thyroid Disease

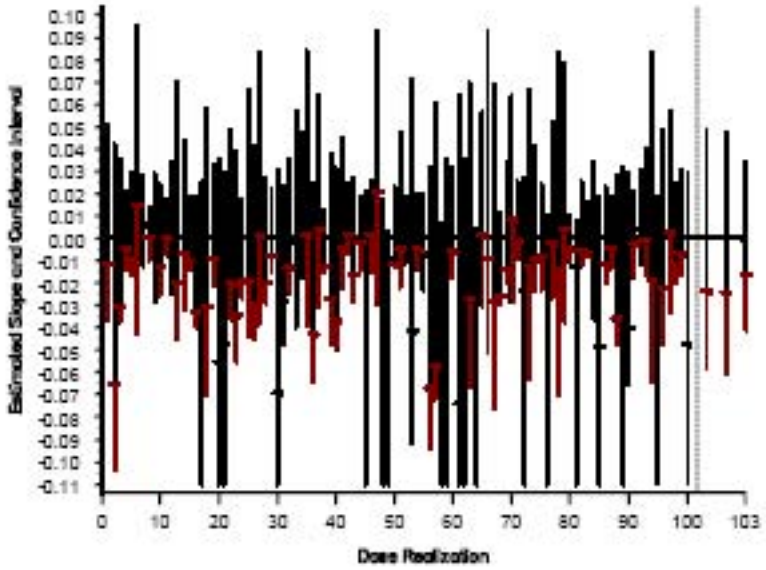
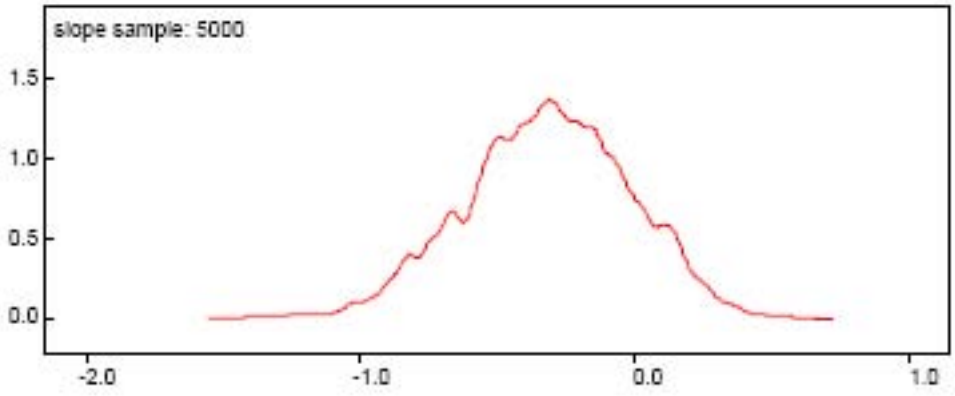


Figure IX.J-2 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –1.5 and 0.5. The estimate was less than or equal to 0 for 4226 of the 5000 replications, implying an empirical one-tailed p-value of 0.85. The median estimate was –0.31, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –1.08 and 0.35. These may be compared to the estimate of –0.17 with confidence interval (–0.68, 0.34) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of autoimmune thyroid disease increased with increasing dose.

Figure IX.J-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Autoimmune Thyroid Disease



K. Hyperthyroidism

K.1. Occurrence of Hyperthyroidism

The primary and alternative definitions for hyperthyroidism were as follows:

- Primary definition: HTDS evaluation or medical records with supporting documentation (161 cases)
- Alternative definition #1: HTDS evaluation or medical records with or without supporting documentation (175 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (196 cases).

There were 161 (4.7%) cases of hyperthyroidism based on the HTDS evaluation or medical records with supporting documentation (Table IX.K-1). An additional 14 (0.4%) living evaluable participants had a diagnosis of hyperthyroidism based on medical records without supporting documentation, and 21 (0.6%) were based on a participant or his/her CATI respondent report. The cumulative incidence of hyperthyroidism was higher for women (9.0%) than men (2.3%).

It is important to understand that these 196 cases included a substantial number of iatrogenic cases (these are discussed below). Since endogenous hyperthyroidism was of particular importance, analyses that focused on cases of non-iatrogenic hyperthyroidism were given particular emphasis in this study.

Table IX.K-1. Basis for Diagnosis of Hyperthyroidism, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	157	9.0	39	2.3	196	5.7
▪ HTDS evaluation	77	4.4	18	1.1	95	2.8
▪ Medical records with supporting documentation	57	3.3	9	0.5	66	1.9
▪ Medical records *without* supporting documentation	12	0.7	2	0.1	14	0.4
▪ Participant/respondent report	11	0.6	10	0.6	21	0.6
No	1572	90.0	1649	97.4	3221	93.6
Unknown	18	1.0	5	0.3	23	0.7
Total	1747	100.0	1693	100.0	3440	100.0

Twenty-three living evaluable participants were classified as "unknown" with regard to diagnosis of hyperthyroidism. These participants did not have a medical record indicating hyperthyroidism, but 13 had a participant report of an unknown thyroid problem, with most indicating it was either an over or under active thyroid for which they took some type of medication. Eight others had no blood draw and for two others a diagnosis of hyperthyroidism could not be ruled out. These 23 participants were included as non-cases in analyses of the dose-response for hyperthyroidism.

One or more possible etiologies were identified for all of the 196 participants with hyperthyroidism. Exogenous thyroid medication was the most common etiology (59.2%) (Table IX.K-2). Graves disease (19.9%) was the second most frequent etiology of hyperthyroidism, followed by uncertain (14.3%). Six of the eight living evaluable participants with hyperthyroidism and an etiology of other were due to possible subacute thyroiditis, while two were due to possible Graves disease.

Table IX.K-2. Etiologies of Hyperthyroidism, by Sex

	Female		Male		Total	
Etiology	No.	%	No.	%	No.	%
Graves disease	32	20.4	7	17.9	39	19.9
Toxic nodular goiter	2	1.3	0	--	2	1.0
Solitary autonomous nodule	1	0.6	1	2.6	2	1.0
Subacute thyroiditis	3	1.9	2	5.1	5	2.6
Silent/post-partum thyroiditis	1	0.6	0	--	1	0.5
Exogenous thyroid medication	102	65.0	14	35.9	116	59.2
Uncertain	13	8.3	15	38.5	28	14.3
Other	8	5.1	0	--	8	4.1
Total with hyperthyroidism	157	100.0	39	100.0	196	100.0

Note: A participant can have >1 etiology

K.1.a. Non-iatrogenic Hyperthyroidism

Since the inclusion of iatrogenic hyperthyroidism might mask an effect of radiation on risk of endogenous hyperthyroidism, an additional disease outcome of non-iatrogenic hyperthyroidism was also defined. A total of 50 living evaluable participants had diagnoses of non-iatrogenic hyperthyroidism based on their HTDS evaluations or on medical records with supporting documentation (Table IX.K-3).

Table IX.K-3. Non-Iatrogenic Hyperthyroidism, by Sex

	Female		Male		Total	
Non-iatrogenic Hyperthyroidism	No.	%	No.	%	No.	%
Yes	37	2.1	13	0.8	50	1.4
No	1710	97.9	1680	99.2	3390	98.5
Total	1747	100.0	1693	100.0	3440	100.0

K.2. Analysis of Hyperthyroidism Risk

K.2.a. Primary Analysis

Of the 161 living evaluable participants with a diagnosis of hyperthyroidism based on the HTDS examination or medical records with supporting documentation, six were out-of-area participants for whom the CIDER program could not calculate dose estimates. The proportions with hyperthyroidism are shown by sex, dose category and basis for diagnosis in Table IX.K-4. The numbers and proportions with diagnoses of non-iatrogenic hyperthyroidism are also shown.

Table IX.K-4. Diagnoses of Hyperthyroidism by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report		Non-iatrogenic Hyperthyroidism (Primary Definition)	
	No.	No.	%	No.	%	No.	%	No.	%
Out of Area	125	6	4.8	6	4.8	7	5.6	2	1.6
< 10	182	10	5.5	12	6.6	13	7.1	5	2.7
10-49	320	27	8.4	29	9.1	29	9.1	6	1.9
50-99	313	30	9.6	32	10.2	36	11.5	9	2.9
100-149	220	9	4.1	10	4.5	12	5.5	2	0.9
150-199	126	11	8.7	14	11.1	16	12.7	0	0.0
200-299	139	13	9.4	15	10.8	15	10.8	4	2.9
300-399	144	14	9.7	14	9.7	15	10.4	4	2.8
400-999	171	13	7.6	13	7.6	13	7.6	5	2.9
1000+	7	1	14.3	1	14.3	1	14.3	0	--
Total	1747	134	7.7	146	8.4	157	9.0	37	2.1

Table IX.K-4. Diagnoses of Hyperthyroidism by Sex, Estimated Dose, and Basis for Diagnosis (continued)

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		1st Alternative Definition: Cases based on HTDS or Med. Rec. with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report		Non-iatrogenic Hyperthyroidism (Primary Definition)	
	No.	No.	%	No.	%	No.	%	No.	%
Out of Area	124	0	--	0	--	0	--	0	--
< 10	186	5	2.7	5	2.7	5	2.7	2	1.1
10-49	314	4	1.3	4	1.3	6	1.9	2	0.6
50-99	310	3	1.0	5	1.6	6	1.9	2	0.6
100-149	171	4	2.3	4	2.3	5	2.9	4	2.3
150-199	109	1	0.9	1	0.9	2	1.8	1	0.9
200-299	148	1	0.7	1	0.7	2	1.4	1	0.7
300-399	160	6	3.8	6	3.8	7	4.4	1	0.6
400-999	154	2	1.3	2	1.3	5	3.2	0	--
1000+	17	1	5.9	1	5.9	1	5.9	0	--
Total	1693	27	1.6	29	1.7	39	2.3	13	0.8

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.K-5 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was 0.011 per Gy; row 1 of Table IX.K-5). The Bonferroni-adjusted 95% confidence interval ranged from less than –0.008 to 0.052, thus the cumulative incidence of hyperthyroidism did not increase significantly with increasing dose ($p = 0.22$). The corresponding estimated background rates for diagnosis of hyperthyroidism were 0.077 with confidence interval (0.060, 0.094) for women and 0.015 with confidence interval (0.006, 0.025) for men. Similar results were obtained when the model was fit by the method of least squares using ungrouped or grouped data (Table IX.K-5, rows 2 and 3).

Table IX.K-5. Summary of Dose-Response Results for Diagnoses of Hyperthyroidism

Row	Outcome	Dose Response Model	Dose Estimates	Exclusions Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation or medical record with documentation)	Linear	Primary	None	MLE	.077 ± .007 (.060, .094)	.015 ± .004 (.006, .025)	.011 ± .015 (<-.008, .052)	0.22
2.	Primary definition	Linear	Primary	None	LSU	.076 ± .006 (.062, .090)	.014 ± .006 (0*, .029)	.018 ± .017 (-.022, .058)	0.15
3.	Primary definition	Linear	Primary	None	LSG	.077 ± .006 (.062, .092)	.015 ± .006 (0*, .030)	.012 ± .019 (-.034, .059)	0.26
4.	Alternative def. #1(HTDS or medical record with or without documentation)	Linear	Primary	None	MLE	.085 ± .007 (.067, .103)	.017 ± .004 (.007, .027)	.007 ± .015 (<-.008, .049)	0.32
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.090 ± .008 (.071, .109)	.022 ± .005 (.011, .034)	.015 ± .018 (<-.011, .063)	0.19

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.K-5. Summary of Dose-Response Results for Diagnoses of Hyperthyroidism (continued)

Row	Outcomes	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Non-iatrogenic hyperthyroidism	Linear	Primary	None	MLE	.022 ± .004 (.012, .033)	.009 ± .003 (.002, .015)	-.004 ± .013 (NE, .019)	0.78
7.	Primary definition	LQ	Primary	None	LSU	.077 ± .007 (.061, .093)	.015 ± .007 (0*, .032)	Lin: .009 ± .029 (–.062, .080) Quad: .007 ± .019 (–.040, .054)	Quad: 0.71
8.	Primary definition	Logistic	Primary	None	MLE	.074 (.058, .095)	.016 (.010, .026)	0.35 ± 0.32 (-.43, 1.12)	0.16
9.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.078 ± .007 (.060, .096)	.016 ± .004 (.006, .027)	.003 ± .018 (<-.021, .051)	0.44
10.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.076 ± .008 (.057, .094)	.014 ± .004 (.004, .024)	.028 ± .027 (-.029, .101)	0.13
11.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.073 ± .007 (.055, .090)	.009 ± .004 (.0004, .018)	.025 ± .016 (<-.006, .067)	0.046

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.K-5. Summary of Dose-Response Results for Diagnoses of Hyperthyroidism (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #1	None	MLE	.080 ± .007 (.062, .098)	.018 ± .004 (.008, .028)	-.005 ± .015 (<-.008, .034)	0.63
13.	Primary definition	Linear	Alt. #2	None	MLE	.079 ± .007 (.062, .097)	.018 ± .004 (.007, .028)	-.002 ± .015 (<-.008, .037)	0.55
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.074 ± .007 (.057, .090)	.013 ± .004 (.005, .022)	.017 ± .015 (<-.007,>.059)	0.11
15.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.074 ± .007 (.058, .090)	.013 ± .004 (.005, .022)	.016 ± .015 (<-.007,> .058)	0.12

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

K.2.b. Alternative Definitions for Diagnosis of Hyperthyroidism

Two alternative definitions for cases of hyperthyroidism were considered. The first alternative added 14 cases with diagnoses based on medical records without supporting documentation, for a total of 175 cases. The resulting dose-response had estimated slope of 0.007 per Gy with Bonferoni-adjusted confidence interval ranging from less than -0.008 to 0.049 per Gy (Table IX.K-5, row 4). The second alternative criterion for defining cases of hyperthyroidism added another 21 participants based solely on a report from the participant or his/her CATI respondent, for a total of 196 cases, estimated slope of 0.015 per Gy, and confidence interval ranging from less than – 0.011 to 0.063 per Gy (Table IX.K-5, row 5). The parameter estimates for the linear dose-response model [1] were not significantly greater than zero ($p = 0.32$ and $p = 0.19$), showing no evidence that the cumulative incidence of hyperthyroidism increased with increasing dose for either alternative criterion of hyperthyroidism.

K.2.b.1. Non-iatrogenic Hyperthyroidism

In the analyses described above, the participants with iatrogenic hyperthyroidism were included among the cases. In order to focus on endogenous outcomes, an additional analysis was performed in which participants with iatrogenic hyperthyroidism only were excluded from the cases. This left a total of 48 cases of non-iatrogenic hyperthyroidism based on the HTDS examination or medical records with supporting documentation among the 3191 in-area evaluable participants. As shown in row 6 of Table IX.K-5, the dose-response was slightly negative, with estimated slope – 0.004 per Gy and upper 95% confidence limit 0.019 per Gy ($p=0.78$).

K.2.c Alternative Dose-Response Functions

As shown in row 7 of Table IX.K-5, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.007 with Bonferroni-adjusted 95% confidence interval ranging from –0.040 to 0.054. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.71$).

In the analysis of hyperthyroidism based on the HTDS examination or medical records with supporting documentation, i.e., the primary criterion for defining cases with hyperthyroidism, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.35 with Bonferroni-adjusted 95% confidence interval ranging from –0.43 to 1.12 (Table IX.K-5, row 8). Thus the cumulative incidence of hyperthyroidism did not increase significantly with increasing dose ($p = 0.16$).

K.2.d. Effect of Excluding Participants in High Dose Categories

As shown in rows 9 and 10 of Table IX.K-5, when participants in high dose categories were excluded, the cumulative incidence of hyperthyroidism did not increase significantly with increasing dose ($p = 0.44$ and $p = 0.13$ when participants with estimated dose > 1000 mGy and > 400 mGy were excluded, respectively).

K.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When the Okanogan and Ferry/Stevens geostrata were excluded, the estimated slope of the sex-stratified linear dose-response model was 0.025 per Gy with Bonferroni-adjusted 95% confidence interval ranging from less than –0.006 to 0.067 per Gy (Table IX.K-5, row 11). While this result might be regarded as evidence that the cumulative incidence of hyperthyroidism increased with increasing dose

among the participants in the remaining geostrata (p = 0.046), it is not considered statistically significant in view of the large number of significance tests that were performed.

K.2.f. Analysis of Hyperthyroidism in Relation to Alternative Dose Estimates

As shown in rows 12 and 13 of Table IX.K-5, the slope of the dose-response was slightly negative when estimated in relation to either of the alternative dose estimates. Thus there was no evidence from these analyses that risk of hyperthyroidism increased significantly with increasing dose (p = 0.63 and p = 0.55 for the first and second alternative dose estimates, respectively).

K.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 14 and 15 of Table IX.K-5, in neither scoping analysis did the cumulative incidence of hyperthyroidism increase significantly with increasing dose (p = 0.11 and p = 0.12 for the first and second scoping analyses, respectively).

K.2.h. Analysis of Hyperthyroidism in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

K.2.h.1. Analysis by Geostratum

As shown in Table IX.P-18, among the 3429 living evaluable in area or out-of-area participants with ultrasound results, the proportions with palpable UDAs ranged from 9/68 (13.2% in the Stevens/Ferry Counties geostratum) to 9/177 (5.1%, Richland) for women, and from 5/63 (7.9%, Okanogan County) to 13/501 (2.6%, Pasco/Kennewick) for men (p = 0.051 for heterogeneity among the nine geostrata). In particular the percentages with palpable UDAs were somewhat higher in the Okanogan and Ferry/Stevens geostrata (12.6% for women, 6.8% for men) than in the remaining geostrata (8.5% and 3.9%, respectively; p = 0.0086). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.K-6. Diagnoses of Hyperthyroidism Based on the HTDS Evaluation or on Medical Records with Supporting Documentation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	13	7.3	173	2	1.2	352	15	4.3
Pasco/Kennewick	508	37	7.3	501	6	1.2	1009	43	4.3
Benton County	376	30	8.0	358	4	1.1	734	34	4.6
Franklin County	73	4	5.5	76	1	1.3	149	5	3.4
Adams County	165	14	8.5	156	2	1.3	321	16	5.0
Walla Walla (city)	133	7	5.3	131	4	3.1	264	11	4.2
Walla Walla County	170	14	8.2	164	1	0.6	334	15	4.5
Okanogan County	75	8	10.7	64	3	4.7	139	11	7.9
Ferry/Stevens Counties	68	7	10.3	70	4	5.7	138	11	8.0
Total	1747	134	7.7	1693	27	1.6	3440	161	4.7

K.2.h.2. Analysis by Dichotomous Exposure Variable

Fifty-six (4.5%) of the 1257 participants included in these analyses had a diagnosis of hyperthyroidism based on the HTDS examination or medical records with supporting documentation (see Table IX.K-7). These included 28/580 (4.8%) in the high exposure group and 28/677 (4.1%) in the low exposure group. The cumulative incidence of hyperthyroidism was not significantly higher in the high exposure group ($p = 0.074$).

Table IX.K-7. Diagnoses of Hyperthyroidism Based on HTDS or Medical Record with Supporting Documentation, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	22	6.3	326	6	1.8	677	28	4.1
High	298	24	8.1	282	4	1.4	580	28	4.8
Total	649	46	7.1	608	10	1.6	1257	56	4.5

The second alternative criterion for defining cases of hyperthyroidism included all possible cases (see section IX.K.1 above). Among the 1257 participants included in these analyses, use of the second alternative added three cases based on medical records without supporting documentation and five others based on a report from the participant or his/her CATI respondent, for a total of 64 (5.1%). Since the number of added cases was small, the logistic regression analysis with adjustment for the effects of sex and age at HTDS examination gave essentially the same results as that based on the primary definition for hyperthyroidism. In particular, the cumulative incidence of hyperthyroidism was not significantly higher in the high exposure group ($p = 0.062$).

K.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of hyperthyroidism; those based on an HTDS diagnosis or on medical records with documented diagnoses, and on the primary dose estimates. Table IX.K-8 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.K-8 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate. Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.K-8, the regression coefficients did not differ significantly between the groups defined by any of the covariates, with the possible exception of estimated NTS dose. The estimated regression coefficient was 0.828 with confidence interval (–0.174, 1.83) for the 1622 participants with estimated NTS dose ≤ 5.3 mGy, compared to –1.18 with confidence interval (–3.58, 1.22) for those with higher estimated NTS doses. The p-value for comparing these two slopes, 0.019, should be interpreted with caution in view of the large number of significance tests that were performed, and of the extensive overlap of the two estimates' confidence intervals.

Table IX.K-8. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Hyperthyroidism

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	.346 ± .325 (–.432, 1.12)	Not Applicable	.282 ± .760 (–1.62, 2.18)	.361 ± .360 (–.538, 1.26)	.92
Prenatal exposure?	1034 / 3191	.346 ± .325 (–.432, 1.12)	.333 ± .328 (–.512, 1.18)	.439 ± .356 (–.501, 1.38)	-.089 ± .774 (–2.13, 1.95)	.52
1st exposure before age 180 days?	1478 / 3191	.346 ± .325 (–.432, 1.12)	.355 ± .329 (–.491, 1.20)	.829 ± .582 (–.706, 2.36)	.136 ± .435 (–1.01, 1.28)	.34
Age at exam > 50?	2001 / 3191	.346 ± .325 (–.432, 1.12)	.392 ± .323 (–.441, 1.23)	.249 ± .564 (–1.24, 1.74)	.471 ± .397 (–.577, 1.52)	.74
NTS ^{131}I dose > 5.3 mGy?	1567 / 3189	.346 ± .325 (–.432, 1.12)	.314 ± .334 (–.547, 1.18)	.828 ± .380 (–.174, 1.83)	–1.18 ± .909 (–3.58, 1.22)	.019
History of any cancer other than thyroid cancer?	248 / 3186	.346 ± .325 (–.432, 1.12)	.384 ± .331 (–.469, 1.24)	.489 ± .345 (–.421, 1.40)	–1.43 ± 2.51 (–8.04, 5.19)	.30
Expanded In-Person Interview?	1212 / 3191	.346 ± .325 (–.432, 1.12)	.463 ± .327 (–.380, 1.31)	.520 ± .547 (–.924, 1.96)	.431 ± .413 (–.659, 1.52)	.90

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.K-9 and IX.K-10 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposures as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for hyperthyroidism.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.K-9 and IX.K-10, with the possible exception of history of diagnostic x-rays of chest or upper body, including mammograms ($p = 0.031$; Table IX.K-9). The estimated dose-response coefficient was markedly negative (–7.82) for the 352 participants without such histories, and not markedly different from zero for the majority of participants (0.432 with confidence interval ranging from –0.407 to 1.27). The statistical significance of this difference must be interpreted with caution due to the large number of such comparisons that were performed. Moreover the difference consists of a very negative dose-response in a minority of participants. Therefore it does not appear that any of the covariates in Tables IX.K-9 and IX.K-10 identified a group in which a clearly significant dose-response was present.

Table IX.K-9. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Hyperthyroidism

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Group 1	P
CAT scan of the upper body?	775 / 3149	.347 ± .325 (–.430, 1.13)	.349 ± .329 (–.497, 1.20)	.400 ± .354 (–.534, 1.33)	.107± .797 (–2.00, 2.21)	.74
Diagnostic x-rays of the head?	1191 / 3155	.356 ± .324 (–.419, 1.13)	.367 ± .323 (–.467, 1.20)	.149 ± .452 (–1.04, 1.34)	.667 ± .480 (–.598, 1.93)	.43
Diagnostic x-rays of the neck?	966 / 3167	.345 ± .327 (–.439, 1.13)	.348 ± .329 (–.500, 1.20)	.190 ± .511 (–1.16, 1.54)	.464 ± .417 (–.637, 1.57)	.68
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	.345 ± .325 (–.433, 1.12)	.347 ± .325 (–.490, 1.18)	–7.82 ± 5.01 (–21.0, 5.41)	.432 ± .318 (–.407, 1.27)	.031
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	.310 ± .334 (–.489, 1.11)	.302 ± .334 (–.559, 1.16)	.107 ± .401 (–.952, 1.17)	.945 ± .639 (–.741, 2.63)	.28
Barium enema?	825 / 3159	.330 ± .327 (–.454, 1.11)	.332 ± .328 (–.512, 1.18)	.586 ± .360 (–.364, 1.53)	–.478 ± .785 (–2.55, 1.59)	.19
Upper GI?	1146 / 3177	.348 ± .324 (–.428, 1.12)	.343 ± .325 (–.494, 1.18)	.541 ± .381 (–.464, 1.55)	–.054 ± .606 (–1.65, 1.54)	.39
Intravenous pyelogram?	398 / 3157	.322 ± .330 (–.468, 1.11)	.322 ± .332 (–.533, 1.18)	.374 ± .346 (–.539, 1.29)	–.082 ± 1.01 (–2.74, 2.57)	.66
Fluoroscopy of the upper body?	246 / 3161	.329 ± .329 (–.458, 1.12)	.338 ± .330 (–.512, 1.19)	.382 ± .336 (–.506, 1.27)	–.250 ± 1.30 (–3.68, 3.18)	.63
Nuclear scan (excluding thyroid scan)?	217 / 3162	.379 ± .322 (–.391, 1.15)	.378 ± .321 (–.449, 1.20)	.399 ± .323 (–.452, 1.25)	–.481 ± 2.20 (–6.29, 5.33)	.68
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	.346 ± .325 (–.432, 1.12)	.342 ± .327 (–.499, 1.18)	.561 ± .422 (–.554, 1.68)	.055 ± .539 (–1.37, 1.48)	.45

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.K-10. Confounding and Effect Modification by Occupational History: Hyperthyroidism

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Any metal industry?	238 / 3191	.346 ± .325 (–.432, 1.12)	.351 ± .325 (–.485, 1.19)	.329 ± .332 (–.546, 1.20)	1.12 ± 1.85 (–3.76, 6.00)	.68
Any nuclear facility?	371 / 3191	.346 ± .325 (–.432, 1.12)	.372 ± .326 (–.468, 1.21)	.372 ± .341 (–.528, 1.27)	.366 ± 1.10 (–2.54, 3.27)	1.00
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	.346 ± .325 (–.432, 1.12)	.355 ± .325 (–.481, 1.19)	.265 ± .372 (–.716, 1.25)	.681 ± .648 (–1.03, 2.39)	.59
Any of the above industries or occupations?	892 / 3191	.346 ± .325 (–.432, 1.12)	.352 ± .325 (–.486, 1.19)	.320 ± .389 (–.706, 1.35)	.430 ± .592 (–1.13, 1.99)	.88

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.K-11 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.K-11. Confounding and Effect Modification by Smoking: Hyperthyroidism

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Cigarettes (unfiltered or filtered)?	1854 / 3183	.344 ± .326 (–.436, 1.12)	.333 ± .325 (–.505, 1.17)	.296 ± .613 (–1.32, 1.91)	.347 ± .382 (–.661, 1.35)	.94
Any of cigarettes, cigar or pipe?	1900 / 3183	.344 ± .326 (–.436, 1.12)	.333 ± .325 (–.505, 1.17)	.294 ± .612 (–1.32, 1.91)	.349 ± .383 (–.661, 1.36)	.94

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

K.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for hyperthyroidism are shown in Figure IX.K-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 81 of the 100 realizations, the confidence interval includes 0 for all 100 realizations. Also shown in Figure IX.K-1 (to the right of realization 100) are the

estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, although the estimated slope was greater than 0 for most realizations.

Figure IX.K-1. Plot of estimated Slope and 95% CI by Dose Realization: Hyperthyroidism

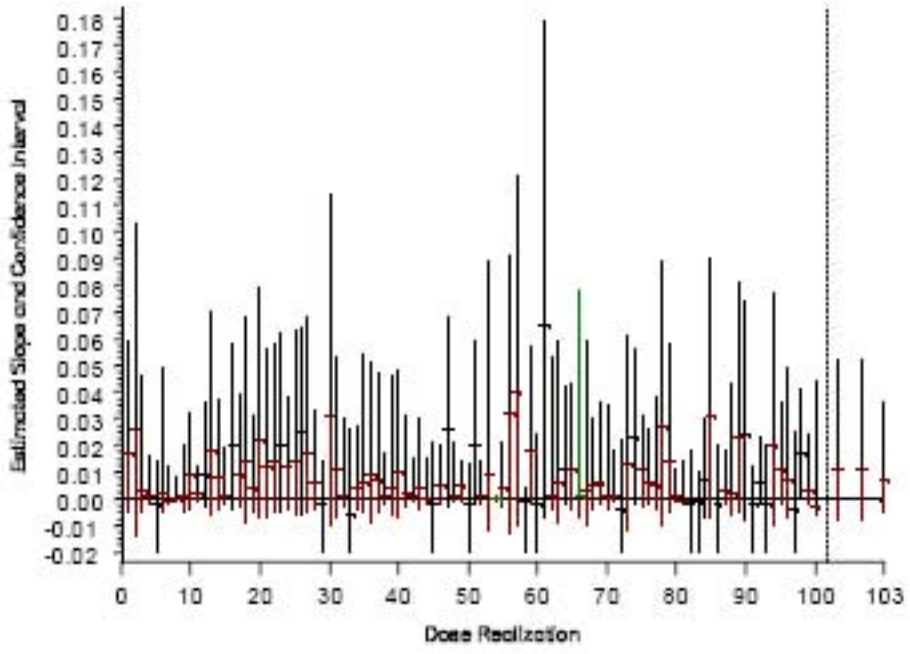
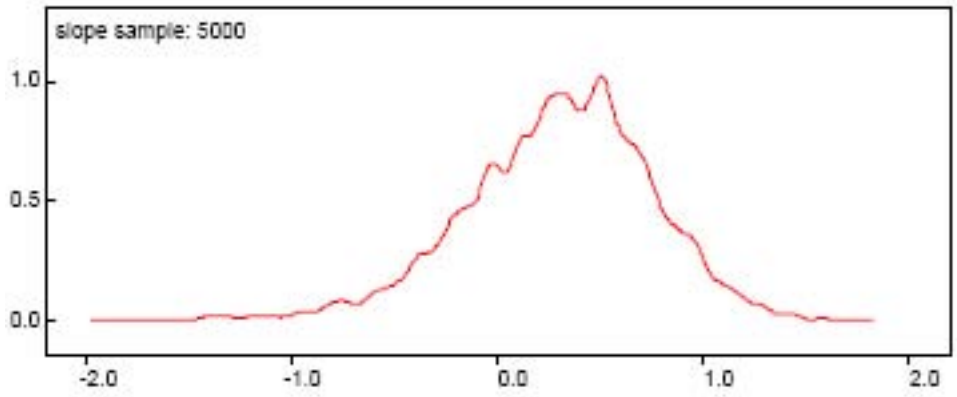


Figure IX.K-2 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –1.0 and 1.5. The estimate was less than or equal to 0 for 1193 of the 5000 replications, implying an empirical one-tailed p-value of 0.24. The median estimate was 0.33, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –0.97 and 1.27. These may be compared to the estimates of 0.35 with the confidence interval (–0.43, 1.12) obtained using the median dose estimate without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of hypothyroidism increased with increasing dose.

Figure IX.K-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Hyperthyroidism



L. Multinodular Thyroid Gland

L.1. Occurrence of Multinodular Thyroid Gland

The primary and alternative definitions for multinodular thyroid gland were as follows:

- Primary definition: HTDS evaluation (95 cases)
- Alternative definition #1: HTDS evaluation or medical records (114 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (115 cases).

Of the 3440 living evaluable participants, 95 (2.8%) had a diagnosis of multinodular thyroid gland based on the HTDS evaluation (Table IX.L-1). An additional 19 (0.6%) living evaluable participants had a diagnosis of multinodular thyroid gland based on medical records, and 1 had a participant/respondent report of multinodular thyroid gland.

Table IX.L-1. Basis for Diagnosis of Multinodular Thyroid Gland, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	90	5.2	25	1.5	115	3.3
▪ HTDS evaluation	73	4.2	22	1.3	95	2.8
▪ Medical record	16	0.9	3	0.2	19	0.6
▪ Participant/respondent report	1	0.1	0	--	1	0.0
No	1656	94.8	1668	98.5	3324	96.6
Unknown	1	0.1	000	--	1	0.0
Total	1747	100.0	1693	100.0	3440	100.0

One living evaluable participant was classified as "unknown" with regard to diagnosis of multinodular thyroid gland. This participant did not have medical record or participant/respondent report indicating multinodular thyroid gland, and did not have an HTDS evaluation due to physician disagreement on the diagnosis, with one physician assigning a diagnosis of multinodular gland while the other assigned a diagnosis of solitary nodule. This participant was included as a non-case in analyses of the dose-response for multinodular thyroid gland.

As shown in Table IX.L-2, the most common etiology of multinodular thyroid gland was other (65.2%), followed by Hashimoto's thyroiditis (32.2%), and hypothyroidism (13.0%).

Table IX.L-2. Etiologies of Multinodular Thyroid Gland, by Sex

	Female		Male		Total	
Etiology	No.	%	No.	%	No.	%
Graves disease	3	3.3	0	--	3	2.6
Hashimoto's thyroiditis	30	33.3	7	28.0	37	32.2
Hypothyroidism	14	15.6	1	4.0	15	13.0
Other	56	62.2	19	76.0	75	65.2
Total with multinodular thyroid gland	90	100.0	25	100.0	115	100.0

Note: A participant can/may have more than one etiology

Of the 75 with an other etiology for multinodular thyroid gland, 47 (62.7%) were unknown/uncertain, 11 (14.7%) were colloid nodule, and 10 (13.3%) were probable/possible Hashimoto's thyroiditis (Table IX.L-3).

Table IX.L-3. "Other" Etiologies of Multinodular Thyroid Gland, by Sex

	Female		Male		Total	
Other Etiologies	No.	%	No.	%	No.	%
Unknown/uncertain	37	66.1	10	52.6	47	62.7
Probable/possible Hashimoto's thyroiditis	7	12.5	3	15.8	10	13.3
Colloid nodules	6	10.7	5	26.3	11	14.7
Colloid goiter	1	1.8	1	5.3	2	2.7
Papillary/follicular cancer	2	3.6	0	--	2	2.7
Possible hypothyroidism	1	1.8	0	--	1	1.3
Probable medical radiation	1	1.8	0	--	1	1.3
Multiple etiologies*	1	1.8	0	--	1	1.3
Total with an other etiology of multinodular thyroid gland	56	100.0	19	100.0	75	100.0

* Includes: 1) adenomatous nodules, 2) focus of papillary cancer, 3) focus of Hashimoto's

L.2. Analysis of Multinodular Thyroid Gland Risk

L.2.a. Primary Analysis

Of the 95 living evaluable participants with a diagnosis of multinodular thyroid gland based on the HTDS examination, 10 were out-of-area participants for whom the CIDER program could not calculate dose estimates. The proportions with multinodular thyroid gland are shown by sex, dose category and basis for diagnosis in Table IX.L-4.

Table IX.L-4. Diagnoses of Multinodular Thyroid Gland by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS Examination		1st Alternative Definition Cases Based on HTDS Examination or Medical Records		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	125	9	7.2	9	7.2	9	7.2
< 10	182	10	5.5	10	5.5	10	5.5
10-49	320	13	4.1	16	5.0	16	5.0
50-99	313	12	3.8	17	5.4	17	5.4
100-149	220	10	4.5	12	5.5	12	5.5
150-199	126	3	2.4	3	2.4	3	2.4
200-299	139	3	2.2	7	5.0	8	5.8
300-399	144	6	4.2	6	4.2	6	4.2
400-999	171	7	4.1	9	5.3	9	5.3
1000+	7	0	--	0	--	0	--
Total	1747	73	4.2	89	5.1	90	5.2

Table IX.L-4. Diagnoses of Multinodular Thyroid Gland by Sex, Estimated Dose, and Basis for Diagnosis (continued)

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS Examination		1st Alternative Definition Cases Based on HTDS Examination or Medical Records		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	124	1	0.8	2	1.6	2	1.6
< 10	186	4	2.2	4	2.2	4	2.2
10-49	314	5	1.6	5	1.6	5	1.6
50-99	310	4	1.3	4	1.3	4	1.3
100-149	171	2	1.2	3	1.8	3	1.8
150-199	109	1	0.9	1	0.9	1	0.9
200-299	148	2	1.4	2	1.4	2	1.4
300-399	160	2	1.3	2	1.3	2	1.3
400-999	154	1	0.6	2	1.3	2	1.3
1000+	17	0	--	0	--	0	--
Total	1693	22	1.3	25	1.5	25	1.5

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.L-5 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was –0.006 per Gy; row 1 of Table IX.L-5). The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.014 per Gy, and the cumulative incidence of multinodular thyroid gland did not increase significantly with increasing dose (p = 0.88). The corresponding estimated background rates for diagnosis of multinodular thyroid gland were 0.040 with confidence interval (0.027, 0.053) for women and 0.014 with confidence interval (0.006, 0.023) for men. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was even more negative than the maximum likelihood estimate (Table IX.L-5, rows 2 and 3), thereby providing no evidence that risk of multinodular thyroid gland increased with increasing dose (p = 0.89 and 0.83).

Table IX.L-5. Summary of Dose-Response Results for Diagnoses of Multinodular Thyroid Gland

Row	Outcome	Dose Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation)	Linear	Primary	None	MLE	.040 ± .005 (.027, .053)	.014 ± .004 (.006, .023)	-.006 ± .016 (NE, .014)	0.88
2.	Primary definition	Linear	Primary	None	LSU	.042 ± .005 (.031, .053)	.016 ± .005 (.005, .027)	-.016 ± .013 (-.046, .015)	0.89
3.	Primary definition	Linear	Primary	None	LSG	.042 ± .005 (.031, .053)	.016 ± .005 (.004, .027)	-.014 ± .015 (-.049, .021)	0.83
4.	Alternative def. #1 (HTDS or medical record)	Linear	Primary	None	MLE	.050 ± .006 (.037, .065)	.016 ± .004 (.006, .025)	-.006 ± .016 (NE, .018)	0.86
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.051 ± .006 (.037, .065)	.016 ± .004 (.006, .025)	-.006 ± .016 (NE, .018)	0.86

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.L-5. Summary of Dose-Response Results for Diagnoses of Multinodular Thyroid Gland (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Primary definition	LQ	Primary	None	LSU	.043 ± .005 (.031, .055)	.017 ± .005 (.004, .029)	Lin: –.021 ± .022 (–.075, .032) Quad: .005 ± .014 (–.031, .040)	Quad: 0.75
7.	Primary definition	Logistic	Primary	None	MLE	.045 (.031, .064)	.015 (.009, .027)	–.82 ± .65 (-2.37, .72)	0.92
8.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.042 ± .005 (.029, .055)	.016 ± .004 (.007, .025)	-.016 ± .014 (NE, >.016)	0.92
9.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.042 ± .006 (.028, .056)	.017 ± .004 (.007, .028)	-.025 ± .023 (<-.059, .035)	0.86
10.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.039 ± .006 (.026, .053)	.015 ± .004 (.005, .024)	-.006 ± .016 (NE, .015)	0.88
11.	Primary definition	Linear	Alt. #1	None	MLE	.040 ± .005 (.027, .053)	.014 ± .004 (.004, .024)	-.006 ± .018 (NE, .010)	0.92

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.L-5. Summary of Dose-Response Results for Diagnoses of Multinodular Thyroid Gland (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #2	None	MLE	.040 ± .005 (.028, .053)	.014 ± .004 (.006, .023)	-.006 ± .010 (NE, .015)	0.86
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.043 ± .005 (.030, .055)	.014 ± .003 (.006, .022)	-.006 ± .015 (NE, .014)	0.88
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.043 ± .005 (.030, .055)	.014 ± .003 (.006, .022)	-.006 ± .015 (NE, >.013)	0.88

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

L.2.b. Alternative Definitions for Diagnosis of Multinodular Thyroid Gland

Two alternative definitions for cases of multinodular thyroid gland were considered. The first alternative added 19 cases with diagnoses based on medical records, for a total of 114 cases. The second added a single case based solely on a report from the participant or his/her CATI respondent, for a total of 115 cases. This last case had an estimated dose of 254 mGy.

As shown in rows 4 and 5 of Table IX.L-5, the slope of the dose-response in the sex-stratified linear model estimated for both alternative definitions of multinodular thyroid gland were nearly identical to the estimate based on the primary definition (estimated slope –0.006 per Gy with Bonferoni-adjusted 95% upper confidence limit 0.018 per Gy). Thus for neither alternative definition did the cumulative incidence of multinodular thyroid gland increase significantly with increasing dose ($p = 0.86$ for both alternatives).

L.2.c. Alternative Dose-Response Functions

As shown in row 6 of Table IX.L-5, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.005 with Bonferroni-adjusted 95% confidence interval ranging from –0.031 to 0.040. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.75$).

In the analysis of multinodular thyroid gland based on the HTDS examination, i.e., the primary criterion for defining cases with multinodular thyroid gland, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –0.82 with Bonferroni-adjusted 95% confidence interval ranging from -2.37 to 0.72 (Table IX.L-5, row 7). Thus the cumulative incidence of multinodular thyroid gland did not increase significantly with increasing dose ($p = 0.92$).

L.2.d. Effect of Excluding Participants in High Dose Categories

Rows 8 and 9 of Table IX.L-5 show the effect of excluding patients in high dose categories from the analysis of the sex-stratified linear dose-response model. When participants with estimated dose > 1000 mGy were excluded from the analysis, the estimated slope of the dose-response decreased to –0.016 per Gy, providing no evidence that the cumulative incidence of multinodular gland increased with increasing dose ($p = 0.92$). Similarly, when participants with estimated dose > 400 mGy were excluded, the estimated slope B was even more negative (–0.025, with Bonferroni-adjusted 95% confidence interval ranging from less than –0.059 to 0.035), providing no evidence that the cumulative incidence increased with increasing dose ($p = 0.86$).

L.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When participants in the Ferry/Stevens geostrata were excluded, the estimated slope B was virtually unchanged (–0.006 per Gy, Table IX.L-5, row 10), providing no evidence that the cumulative incidence of multinodular thyroid gland increased with increasing dose ($p = 0.88$).

L.2.f. Analysis of Multinodular Thyroid Gland in Relation to Alternative Dose Estimates

Rows 11 and 12 of Table IX.L-5 show that the estimated dose-response was almost unchanged when the two alternative sets of dose estimates were used in place of the primary doses. In particular there

was no evidence that cumulative incidence of multinodular thyroid gland increased with increasing doses from either of the alternative dose sets (p = 0.92 and p= 0.86 for alternative dose sets 1 and 2, respectively).

L.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As summarized in rows 13 and 14 of Table IX.L-5, in neither scoping analysis did the cumulative incidence of multinodular thyroid gland increase significantly with increasing dose (p = 0.88 for both scoping analyses).

L.2.h. Analysis of Multinodular Thyroid Gland in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

L.2.h.1. Analysis by Geostratum

As shown in Table IX.L-6, the proportions of participants with multinodular thyroid gland (from the HTDS examination) ranged from 6/75 (8.0%) in the Okanogan geostratum to 0/179 (0%) in the Richland geostratum for women, and from 5/156 (3.2%) in the Adams geostratum to 0/70 (0%) in the Ferry/Stevens geostratum for men. The heterogeneity among the nine geostrata was not statistically significant (p=0.058). The proportions with multinodular thyroid gland were somewhat higher for women in the Okanogan and Ferry/Stevens geostrata (7.0%) compared to the other strata (3.9%), but this was not the case for men (0.7% for Okanogan and Ferry/Stevens versus 1.3% for the others, p = 0.29).

Table IX.L-6. Diagnoses of Multinodular Thyroid Gland Based on the HTDS Evaluation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	0	--	173	4	2.3	352	4	1.1
Pasco/Kennewick	508	17	3.3	501	2	0.4	1009	19	1.9
Benton County	376	16	4.3	358	3	0.8	734	19	2.6
Franklin County	73	2	2.7	76	2	2.6	149	4	2.7
Adams County	165	8	4.8	156	5	3.2	321	13	4.0
Walla Walla (city)	133	10	7.5	131	1	0.8	264	11	4.2
Walla Walla County	170	10	5.9	164	4	2.4	334	14	4.2
Okanogan County	75	6	8.0	64	1	1.6	139	7	5.0
Ferry/Stevens Counties	68	4	5.9	70	0	--	138	4	2.9
Total	1747	73	4.2	1693	22	1.3	3440	95	2.8

L.2.h.2. Analysis by Dichotomous Exposure Variable

Forty-six (3.7%) of the 1257 participants included in these analyses had a diagnosis of multinodular thyroid gland based on the HTDS examination (see Table IX.L-7). These included 19/580 (3.3%) in the high exposure group and 27/677 (4.0%) in the low exposure group. Thus the cumulative incidence of multinodular thyroid gland was not significantly higher in the high exposure group (p = 0.74).

Table IX.L-7. Diagnoses of Multinodular Thyroid Gland Based on HTDS Examination, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	23	6.6	326	4	1.2	677	27	4.0
High	298	16	5.4	282	3	1.1	580	19	3.3
Total	649	39	6.0	608	7	1.2	1257	46	3.7

L.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. These analyses were based on the primary definition of multinodular thyroid gland (HTDS diagnosis), and on the primary dose estimates. Table IX.L-8 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.L-8 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate. Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results.

The analyses of effect modification address the question of whether the dose-response might vary according to other characteristics of the study participants. This was tested by comparing the estimated regression coefficients for the groups defined by each covariate. As shown in Table IX.L-8, the regression coefficients did not differ significantly between the groups defined by any of the covariates. For two covariates the effect modification approached statistical significance: age at first exposure to Hanford's ^{131}I within the HEDR domain ($p = 0.061$), and estimated NTS dose ($p = 0.053$). However, for neither covariate was there evidence of a significant dose-response within a subgroup of participants. In fact for both of these covariates, the difference was due primarily to a very negative regression coefficient in one group.

Table IX.L-8. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Multinodular Thyroid Gland

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted	Adjusted for Confounding	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1622 / 3191	−.824 ± .647 (−2.37, .724)	Not Applicable	−1.97 ± 1.57 (−5.89, 1.94)	−.513 ± .698 (−2.26, 1.23)	.37
Prenatal exposure?	1034 / 3191	−.824 ± .647 (−2.37, .724)	−.862 ± .656 (−2.55, .828)	−.740 ± .751 (−2.72, 1.24)	−1.21 ± 1.33 (−4.72, 2.30)	.76
1st exposure before age 180 days?	1478 / 3191	−.824 ± .647 (−2.37, .724)	−.840 ± .653 (−2.52, .843)	.319 ± .824 (−1.86, 2.49)	−2.42 ± 1.25 (−5.72, .874)	.052
Age at exam > 50?	2001 / 3191	−.824 ± .647 (−2.37, .724)	−.672 ± .641 (−2.32, .978)	−.970 ± 1.16 (−4.02, 2.08)	−.521 ± .774 (−2.56, 1.52)	.74
NTS ^{131}I dose > 5.3 mGy?	1567 / 3189	−.824 ± .647 (−2.37, .724)	−.750 ± .656 (−2.44, .941)	.063 ± .681 (−1.73, 1.86)	−2.93 ± 1.54 (−7.00, 1.15)	.053
History of any cancer other than thyroid cancer?	248 / 3186	−.823 ± .646 (−2.37, .724)	−.828 ± .647 (−2.50, .839)	−.686 ± .670 (−2.45, 1.08)	−2.52 ± 2.84 (−10.0, 4.98)	.48
Expanded In-Person Interview?	1212 / 3191	−.824 ± .647 (−2.37, .724)	−.549 ± .640 (−2.20, 1.10)	−.366 ± .796 (−2.47, 1.73)	−.870 ± 1.13 (−3.85, 2.11)	.71

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Tables IX.L-9 and IX.L-10 display similar results from analyses including history of medical or dental x-ray exposure or of occupational exposure as potential confounding or effect modifying factors. The estimates of the regression coefficient calculated with adjustment for confounding are all close to the unadjusted estimates. Thus there was no evidence that a confounding effect of any of these covariates has obscured a positive dose-response for hyperthyroidism.

There is no evidence of any statistically significant effect modification by any of the covariates in Tables IX.L-9 and IX.L-10, with the possible exception of history of diagnostic x-rays of chest or upper body, including mammograms ($p = 0.033$; Table IX.L-9). The estimated dose-response coefficient was markedly negative (−13.3) for the 352 participants without such histories, but closer to zero for the majority of participants (−0.568). The statistical significance of this difference must be interpreted with caution due to the large number of such comparisons that were performed. Moreover the difference consists of a very negative dose-response in a minority of participants, compared to a less negative coefficient in the remaining participants. Therefore it does not appear that any of the covariates in Tables IX.L-9 and IX.L-10 identified a group in which a clearly significant dose-response was present.

Table IX.L-9. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Multinodular Thyroid Gland

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
CAT scan of the upper body?	775 / 3149	−.895 ± .659 (−2.47, .684)	−.866 ± .656 (−2.56, .823)	−1.19 ± .791 (−3.28, .895)	.182 ± 1.27 (−3.17, 3.54)	.37
Diagnostic x-rays of the head?	1191 / 3155	−.754 ± .641 (−2.29, .780)	−.704 ± .636 (−2.34, .934)	−.647 ± .835 (−2.85, 1.56)	−.779 ± .98 (−3.36, 1.80)	.62
Diagnostic x-rays of the neck?	966 / 3167	−.813 ± .645 (−2.36, .731)	−.794 ± .643 (−2.45, .864)	−.688 ± .785 (−2.76, 1.38)	−1.00 ± 1.15 (−4.03, 2.03)	.82
Diagnostic x-rays of chest or upper body, including mammograms?	2821 / 3173	−.824 ± .646 (−2.37, .723)	−.785 ± .645 (−2.45, .876)	−13.3 ± 8.01 (−34.4, 7.83)	−.568 ± .62 (−2.21, 1.08)	.033
Diagnostic x-rays of the stomach or mid-back?	692 / 3120	−.885 ± .663 (−2.47, .702)	−.900 ± .662 (−2.61, .807)	−.729 ± .686 (−2.54, 1.08)	−2.28 ± 2.23 (−8.17, 3.60)	.48
Barium enema?	825 / 3159	−.790 ± .644 (−2.33, .752)	−.789 ± .644 (−2.45, .871)	−.473 ± .704 (−2.33, 1.38)	−1.79 ± 1.44 (−5.58, 2.00)	.39
Upper GI?	1146 / 3177	−.818 ± .646 (−2.36, .727)	−.821 ± .645 (−2.48, .841)	−.316 ± .706 (−2.18, 1.55)	−1.98 ± 1.29 (−5.38, 1.41)	.24
Intravenous pyelogram?	398 / 3157	−.896 ± .662 (−2.48, .689)	−.888 ± .663 (−2.59, .819)	−587 ± .658 (−2.32, 1.15)	−4.13 ± 2.86 (−11.7, 3.42)	.16
Fluoroscopy of the upper body?	246 / 3161	−.876 ± .659 (−2.45, .701)	−.880 ± .659 (−2.58, .818)	−.672 ± .657 (−2.41, 1.06)	−4.68 ± 3.96 (−15.1, 5.75)	.22
Nuclear scan (excluding thyroid scan)?	217 / 3162	−.888 ± .660 (−2.47, .692)	−.868 ± .660 (−2.57, .832)	−.727 ± .654 (−2.45, .999)	−6.45 ± 6.18 (−22.8, 9.84)	.24
Dental x-rays that did not usually include a lead shield over the neck area?	1648 / 3191	−.824 ± .647 (−2.37, .724)	−.828 ± .649 (−2.50, .842)	−2.36 ± 1.16 (−5.43, .709)	.134 ± .67 (−1.64, 1.91)	.057

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.L-10. Confounding and Effect Modification by Occupational History: Multinodular Thyroid Gland

Have You Ever Worked in Any of the Following? (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Any metal industry?	238 / 3191	−.824 ± .647 (−2.37, .724)	−.814 ± .647 (−2.48, .852)	−.814 ± .647 (−2.52, .892)	--*	--
Any nuclear facility?	371 / 3191	−.824 ± .647 (−2.37, .724)	−.774 ± .649 (−2.45, .897)	−.753 ± .686 (−2.56, 1.06)	−.947 ± 1.98 (−6.17, 4.28)	.93
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3191	−.824 ± .647 (−2.37, .724)	−.876 ± .651 (−2.55, .802)	−.753 ± .664 (−2.50, .998)	−2.82 ± 3.22 (−11.3, 5.68)	.48
Any of the above industries or occupations?	892 / 3191	−.824 ± .647 (−2.37, .724)	−.746 ± .645 (−2.41, .914)	−.570 ± .674 (−2.35, 1.21)	−1.95 ± 2.02 (−7.29, 3.39)	.49

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.
* Dose-response coefficient not estimable as none of the living evaluable in-area participants with a diagnosis of multinodular thyroid gland ever worked in any metal industry.

Table IX.L-11 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.L-11. Confounding and Effect Modification by Smoking: Multinodular Thyroid Gland

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted	Adjusted for Confounding	Including Effect Modification		P
				Group 0	Group 1	
Cigarettes (unfiltered or filtered)?	1854 / 3183	−.805 ± .647 (−2.35, .744)	−.804 ± .647 (−2.47, .863)	−.053 ± .822 (−2.22, 2.12)	−1.66 ± 1.04 (−4.41, 1.09)	.22
Any of cigarettes, cigar or pipe?	1900 / 3183	−.805 ± .647 (−2.35, .744)	−.804 ± .647 (−2.47, .863)	.036 ± .814 (−2.11, 2.18)	−1.75 ± 1.05 (−4.51, 1.01)	.17

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

L.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for multinodular thyroid gland are shown in Figure IX.L-1 for each of the 100 dose realizations produced by the CIDER model. The

confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. The point estimate of the slope was greater than 0 for only 8 of the 100 realizations, and the confidence interval included 0 for all 100 realizations. Also shown in Figure IX.L-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for most of the realizations the estimated slope was less than 0.

Figure IX.L-1. Plot of Estimated Slope and 95% CI by Dose Realization: Multinodular Thyroid Gland

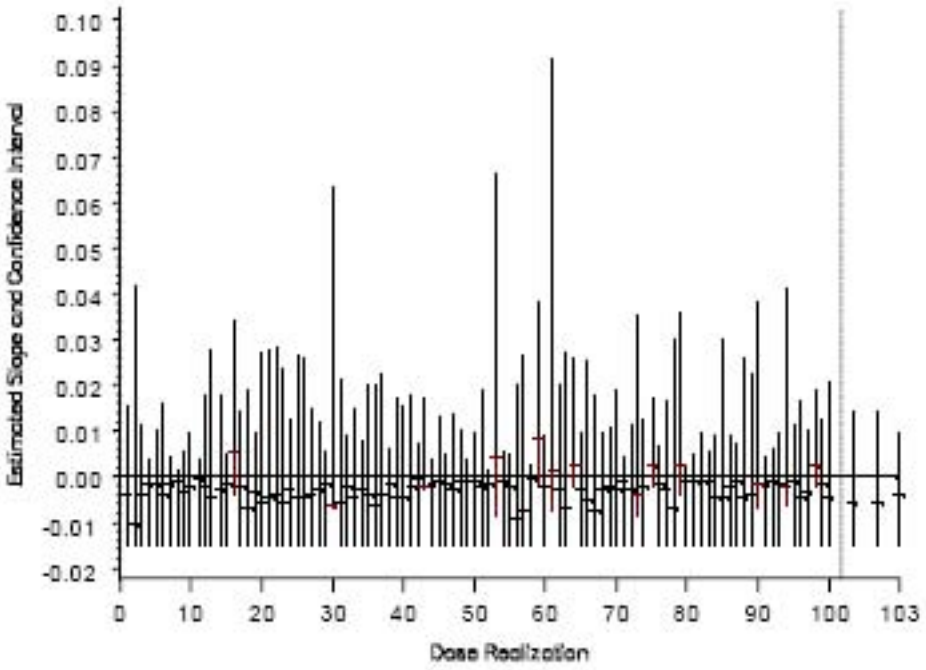
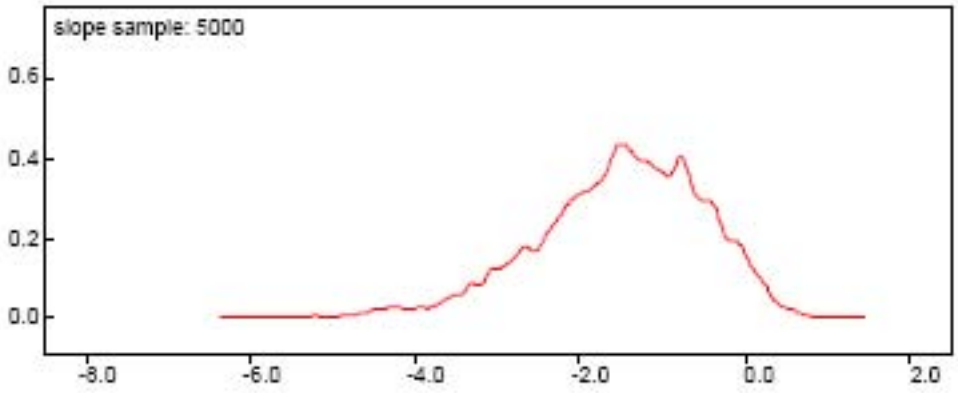


Figure IX.L-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –5.0 and 1.0. The estimate was less than or equal to 0 for 4770 of the 5000 replications, implying an empirical one-tailed p-value of 0.89. The median estimate was –1.41, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –4.37 and 0.39. These may be compared to the estimate of –0.82 with confidence interval (–2.37, 0.72) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of multinodular thyroid gland increased with increasing dose.

Figure IX.L-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Multinodular Thyroid Gland



M. Simple Goiter

M.1. Occurrence of Simple Goiter

The primary and alternative definitions for simple goiter were as follows:

- Primary definition: HTDS evaluation (14 cases)
- Alternative definition #1: HTDS evaluation or medical records (42 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (70 cases).

The diagnosis of simple goiter was uncommon, with only 14 (0.4%) living evaluable participants having this diagnosis based on HTDS evaluation, 28 (0.8%) based on medical records, and 28 (0.8%) based on a report by the participant or his/her CATI respondent (Table IX.M-1). It should be noted that since this outcome is based solely on physical examination, diagnoses based on medical records are subject to wide variability since exams were done by many different types of providers with differing levels of consistency and frequency and differing criteria for simple goiter. Simple goiter was more commonly diagnosed among women than men.

Table IX.M-1. Basis for Diagnosis of Simple Goiter, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	62	3.5	8	0.5	70	2.0
▪ HTDS evaluation	9	0.5	5	0.3	14	0.4
▪ Medical record	27	1.5	1	0.1	28	0.8
▪ Participant/respondent report	26	1.5	2	0.1	28	0.8
No	1684	96.4	1685	99.5	3369	97.9
Unknown	1	0.1	0	--	1	0.0
Total	1747	100.0	1693	100.0	3440	100.0

One living evaluable participant was classified as "unknown" with regard to diagnosis of simple goiter. This participant did not have a medical record indicating simple goiter, but had a participant report of an unknown diagnosis which might have been goiter. This participant was included as a non-case in analyses of the dose-response for simple goiter.

In 30.0% of the cases, simple goiter had one or more of the following etiologies: Graves disease, Hashimoto's thyroiditis, hypothyroidism and/or hyperthyroidism (Table IX.M-2).

Table IX.M-2. Etiologies of Simple Goiter, by Sex

	Female		Male		Total	
Etiology	No.	%	No.	%	No.	%
Graves disease	9	14.5	0	--	9	12.9
Hashimoto's thyroiditis	6	9.7	2	25.0	8	11.4
Hypothyroidism	6	9.7	2	25.0	8	11.4
Hyperthyroidism	1	1.6	0	--	1	1.4
Other	43	69.4	6	75.0	49	70.0
Total with simple goiter	62	100.0	8	100.0	70	100.0

Note: A participant can have >1 etiology

Of those with an other etiology of simple goiter, 44 (89.8%) had no certain etiology, while 4 (8.2%) were due to probable/possible Hashimoto's, and 1 (2.0%) to possible Graves disease (Table IX.M-3).

Table IX.M-3. "Other" Etiologies of Simple Goiter, by Sex

	Female		Male		Total	
Etiology	No.	%	No.	%	No.	%
Uncertain/unknown	39	90.7	5	83.3	44	89.8
Probable/possible Hashimoto's	3	7.0	1	16.7	4	8.2
Probable Graves disease	1	2.3	0	--	1	2.0
Total with an other etiology of simple goiter	43	100.0	6	100.0	49	100.0

M.2. Analysis of Simple Goiter Risk

M.2.a. Primary Analysis

All of the 14 living evaluable participants with a diagnosis of simple goiter based on the HTDS examination, were in-area participants. The proportions with simple goiter are shown by sex, dose category and basis for diagnosis in Table IX.M-4.

Table IX.M-4. Diagnoses of Simple Goiter by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS examination		1st Alternative Definition: Cases Based on HTDS Examination or Medical Records		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	125	0	--	2	1.6	5	4.0
< 10	182	1	0.5	3	1.6	7	3.8
10-49	320	1	0.3	8	2.5	10	3.1
50-99	313	2	0.6	5	1.6	10	3.2
100-149	220	3	1.4	5	2.3	8	3.6
150-199	126	0	--	2	1.6	3	2.4
200-299	139	1	0.7	2	1.4	5	3.6
300-399	144	1	0.7	4	2.8	7	4.9
400-999	171	0	--	5	2.9	7	4.1
1000+	7	0	--	0	--	0	--
Total	1747	9	0.5	36	2.1	62	3.5

B. Male

Thyroid Radiation Dose (mGy	Living Evaluable Male	Primary Definition: Cases Based on HTDS Examination		1st Alternative Definition: Cases Based on HTDS Examination or Medical Records		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%	No.	%
Out of Area	124	0	--	0	--	0	--
< 10	186	1	0.5	1	0.5	2	1.1
10-49	314	1	0.3	1	0.3	1	0.3
50-99	310	1	0.3	2	0.6	3	1.0
100-149	171	1	0.6	1	0.6	1	0.6
150-199	109	0	--	0	--	0	--
200-299	148	0	--	0	--	0	--
300-399	160	0	--	0	--	0	--
400-999	154	1	0.6	1	0.6	1	0.6
1000+	17	0	--	0	--	0	--
Total	1693	5	0.3	6	0.4	8	0.5

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.M-5 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was –0.001 per Gy (row 1 of Table IX.M-5). The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.012 per Gy, and the cumulative incidence of simple goiter did not increase significantly with increasing dose ($p = 0.74$). The corresponding estimated background rates for diagnosis of simple goiter were 0.006 with confidence interval (0.001, 0.011) for women and 0.003 with confidence interval (0, 0.008) for men. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was even more negative than the maximum likelihood estimate (Table IX.M-5, rows 2 and 3), thereby providing no evidence that risk of simple goiter increased with increasing dose ($p = 0.79$ and 0.70) for the ungrouped and grouped data, respectively.

Table IX.M-5. Summary of Dose-Response Results for Diagnoses of Simple Goiter

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimates Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation)	Linear	Primary	None	MLE	.006 ± .002 (.001, .011)	.003 ± .002 (0*, .008)	–.001 ± .008 (NE, .012)	0.74
2.	Primary definition	Linear	Primary	None	LSU	.006 ± .002 (.002, .011)	.004 ± .002 (0*, .009)	–.004 ± .005 (–.017, .008)	0.79
3.	Primary definition	Linear	Primary	None	LSG	.006 ± .002 (.002, .011)	.004 ± .002 (0*, .009)	-.003 ± .006 (-.018, .011)	0.70
4.	Alternative def. #1 (HTDS or medical record)	Linear	Primary	None	MLE	.021 ± .004 (.012, .031)	.004 ± .002 (-.001, .009)	-.002 ± .009 (NE, .019)	0.68
5.	Alternative def. #2 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.036 ± .005 (.023, .048)	.005 ± .002 (0*, .011)	-.002 ± .011 (NE, .018)	0.74

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.M-5. Summary of Dose-Response Results for Diagnoses of Simple Goiter (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Primary definition	LQ	Primary	None	LSU	.006 ± .002 (.001, .011)	.004 ± .002 (0*, .009)	Lin: –.005 ± .009 (–.028, .017) Quad: .001 ± .006 (–.014, .016)	Quad: 0.88
7.	Primary definition	Logistic	Primary	None	MLE	.007 (.003, .018)	.004 (.001, .013)	–1.56 ± 1.83 (-5.94, 2.81)	0.83
8.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.006 ± .002 (.001, .011)	.004 ± .002 (0*, .009)	-.004 ± .008 (NE, .014)	0.80
9.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.007 ± .003 (0*, .015)	.003 ± .002 (0*, .008)	-.009 ± .016 (NE, .024)	0.84
10.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.006 ± .002 (.000, .011)	.003 ± .002 (0*, .008)	-.001 ± .008 (NE, .015)	0.70
11.	Primary definition	Linear	Alt. #1	None	MLE	.006 ± .002 (.001, .010)	.003 ± .002 (-.001, .008)	-.001 ± .005 (<-.001, .014)	0.55

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.M-5. Summary of Dose-Response Results for Diagnoses of Simple Goiter (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions/ Additional Inclusions	Method of Analysis	Estimates Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #2	None	MLE	.006 ± .002 (.001, .010)	.003 ± .002 (0*, .008)	-.001 ± .005 (<-.002, .016)	0.56
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.005 ± .002 (.001, .010)	.003 ± .002 (0*, .007)	-.001 ± .008 (NE, .014)	0.71
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.005 ± .002 (.001, .010)	.003 ± .002 (-.001, .007)	-.001 ± .008 (NE, >.014)	0.71

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

M.2.b. Alternative Definitions for Diagnosis of Simple Goiter

Two alternative definitions for cases of simple goiter were considered. The first alternative added 28 cases with diagnoses based on medical records, for a total of 42 cases. The second added another 28 cases based solely on a report from the participant or his/her CATI respondent, for a total of 70 cases. As shown in rows 4 and 5 of Table IX.M-5, for neither alternative definition was there evidence that the cumulative incidence of simple goiter increased with increasing dose ($p = 0.68$ and 0.74 for the first and second alternative analyses, respectively).

M.2.c. Alternative Dose-Response Functions

As shown in row 6 of Table IX.M-5, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.001 with Bonferroni-adjusted 95% confidence interval ranging from –0.014 to 0.016. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.88$).

In the analysis of simple goiter based on the HTDS examination, i.e., the primary criterion for defining cases with simple goiter, the regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –1.56 with Bonferroni-adjusted 95% confidence interval ranging from –5.94 to 2.81. Thus the cumulative incidence of simple goiter did not increase significantly with increasing dose ($p = 0.83$; Table IX.M-5, row 7).

M.2.d. Effect of Excluding Participants in High Dose Categories

Rows 8 and 9 of Table IX.M-5 show the effect of excluding patients in high dose categories from the analysis of the sex-stratified linear dose-response model. When participants with estimated dose > 1000 mGy were excluded from the analysis, the estimated slope of the dose-response decreased to –0.004 per Gy, providing no evidence that the cumulative incidence of simple goiter increased with increasing dose ($p = 0.80$). Similarly, when participants with estimated dose > 400 mGy were excluded, the estimated slope B was even more negative (–0.009 per Gy), providing no evidence that the cumulative incidence increased with increasing dose ($p = 0.84$).

M.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When participants in the Okanogan and Ferry/Stevens geostrata were excluded the estimated slope B was essentially unchanged at –0.001 per Gy, providing no evidence that the cumulative incidence of simple goiter increased significantly with increasing dose ($p = 0.70$; Table IX.M-5, row 10).

M.2.f. Analysis of Simple Goiter in Relation to Alternative Dose Estimates

As shown in rows 11 and 12 of Table IX.M-5, substituting either of the alternative sets of dose estimates for the primary doses caused very little change in the estimated slope of the dose-response. In particular there was no evidence that cumulative incidence of simple goiter increased with increasing doses from either of the alternative dose sets ($p = 0.55$ and $p = 0.56$ for alternative dose sets 1 and 2, respectively).

M.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. The results of both scoping analyses (Table IX.M-5, rows 13 and 14) were very similar to those of the primary analysis of the in-area participants (Table IX.M-5, row 1). In particular both estimates of the slope were slightly less than zero, providing no evidence that the cumulative incidence of simple goiter increased with increasing dose ($p = 0.71$ for both scoping analyses).

M.2.h. Analysis of Simple Goiter in Relation to Alternative Representations of Exposure

In analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

M.2.h.1. Analysis by Geostratum

There were too few participants (14) with diagnoses of simple goiter (based on the HTDS examination) for a definitive conclusion regarding heterogeneity among the geostrata (see Table IX.M-6). Therefore, the analysis was based on the second alternative definition of simple goiter, i.e., including all diagnoses or reports of simple goiter. The results are shown in Table IX.M-7 below. There was no significant heterogeneity among the nine geostrata ($p=0.26$). The percentages with simple goiter were somewhat higher in the Okanogan and Ferry/Stevens geostrata (5.6% for women, 1.5% for men) than in the remaining geostrata (3.4% and 0.4%), but this heterogeneity between combined geostrata was also not statistically significant ($p=0.095$).

Table IX.M-6. Diagnoses of Simple Goiter Based on the HTDS Evaluation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	1	0.6	173	2	1.2	352	3	0.9
Pasco/Kennewick	508	2	0.4	501	1	0.2	1009	3	0.3
Benton County	376	3	0.8	358	1	0.3	734	4	0.5
Franklin County	73	0	--	76	0	--	149	0	--
Adams County	165	0	--	156	0	--	321	0	--
Walla Walla (city)	133	0	--	131	0	--	264	0	--
Walla Walla County	170	2	1.2	164	0	--	334	2	0.6
Okanogan County	75	0	--	64	1	1.6	139	1	0.7
Ferry/Stevens Counties	68	1	1.5	70	0	--	138	1	0.7
Total	1747	9	0.5	1693	5	0.3	3440	14	0.4

Table IX.M-7. Diagnoses of Simple Goiter Based on Any Source, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	6	3.4	173	2	1.2	352	8	2.3
Pasco/Kennewick	508	22	4.3	501	2	0.4	1009	24	2.4
Benton County	376	13	3.5	358	2	0.6	734	15	2.0
Franklin County	73	3	4.1	76	0	--	149	3	2.0
Adams County	165	2	1.2	156	0	--	321	2	0.6
Walla Walla (city)	133	4	3.0	131	0	--	264	4	1.5
Walla Walla County	170	4	2.4	164	0	--	334	4	1.2
Okanogan County	75	3	4.0	64	1	1.6	139	4	2.9
Ferry/Stevens Counties	68	5	7.4	70	1	1.4	138	6	4.3
Total	1747	62	3.5	1693	8	0.5	3440	70	2.0

M.2.h.2. Analysis by Dichotomous Exposure Variable

See section VIII.B.3.b.2 above for a description of the high and low exposure categories. Only five (0.4%) of the 1257 participants included in these analyses had a diagnosis of simple goiter based on the HTDS examination (see Table IX.M-8). This was too few for a meaningful comparison between the high and low exposure groups. Therefore the analysis was based on the second alternative definition for diagnoses of simple goiter (section IX.M.1, above), i.e., any diagnosis based on HTDS, medical records, or participant or CATI respondent report. As shown in Table IX.M-9, 24 (1.9%) of the 1257 participants had diagnoses of simple goiter based on this alternative criterion, including 9/580 (1.6%) and 15/677 (2.2%) in the high and low exposure groups, respectively. The cumulative incidence of simple goiter based on this alternative definition was not significantly elevated in the high exposure group ($p = 0.75$).

Table IX.M-8. Diagnoses of Simple Goiter Based on HTDS Examination, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	1	0.3	326	2	0.6	677	3	0.4
High	298	1	0.3	282	1	0.4	580	2	0.3
Total	649	2	0.3	608	3	0.5	1257	5	0.4

Table IX.M-9. Diagnoses of Simple Goiter Based on Any Source, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	13	3.7	326	2	0.6	677	15	2.2
High	298	8	2.7	282	1	0.4	580	9	1.6
Total	649	21	3.2	608	3	0.5	1257	24	1.9

M.2.i. Confounding and Effect Modification

There were too few participants with diagnoses of simple goiter to permit meaningful analysis of confounding or effect modification.

M.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for simple goiter are shown in Figure IX.M-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. The point estimate of the slope was greater than zero for only 13 of the 100 realizations, and the confidence interval included zero for all 100 realizations. Also shown in Figure IX.M-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for most of the realizations the estimated slope was less than 0.

Figure IX.M-1. Plot of Estimated Slope and 95% CI by Dose Realization: Simple Goiter

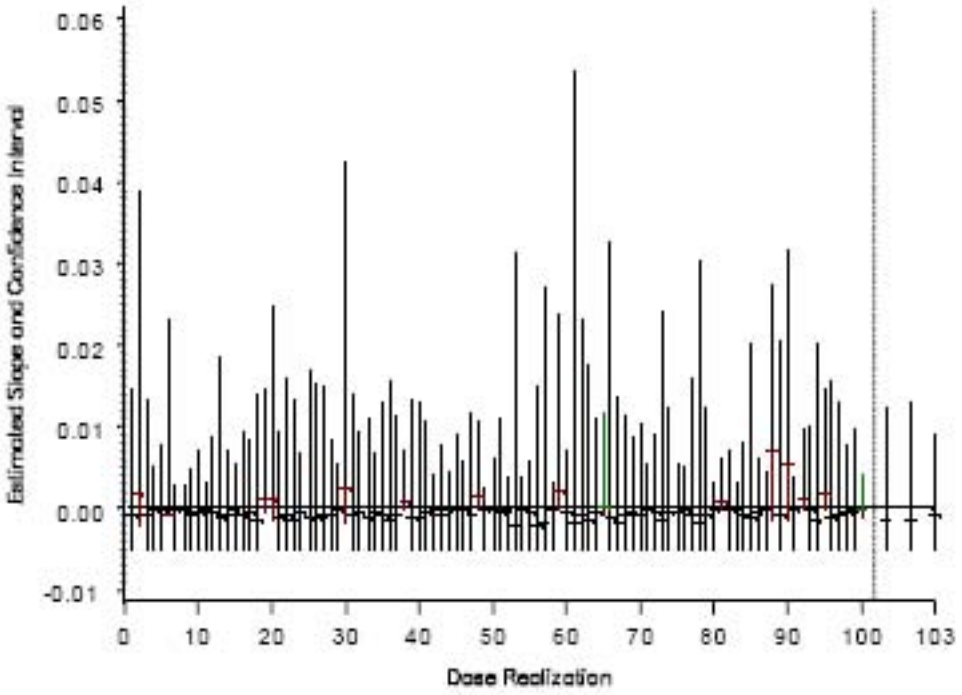
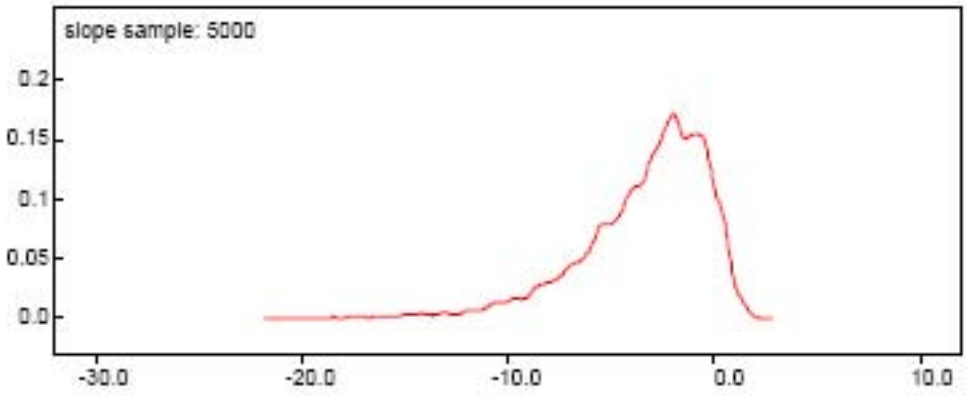


Figure IX.M-2 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –15.0 and 2.0. The estimate was less than or equal to 0 for 4536 of the 5000 replications, implying an empirical one-tailed p-value of 0.91. The median estimate was –2.63, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval ranging from –14.8 to 1.16. These may be compared to the estimate of –1.56 with confidence interval (–5.94, 2.81) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of simple goiter increased with increasing dose.

Figure IX.M-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Simple Goiter



N. Other Thyroid Disease

N.1. Occurrence of Other Thyroid Disease

The primary and alternative definitions for other thyroid disease were as follows:

- Primary definition: HTDS examination or medical records with supporting documentation (4 cases)
- Alternative definition #1: HTDS examination or medical records with or without supporting documentation (6 cases)
- Alternative definition #2: Any diagnosis or participant/respondent report (26 cases).

Four living evaluable participants, all in the in-area group, had diagnoses of other thyroid disease based on their HTDS examinations or medical records with supporting documentation. These included two cases of subacute thyroiditis in women with estimated doses of 342 and 336 mGy; one case of familial thyroglobulin binding deficiency in a male with an estimated dose 102 mGy; and a case of secondary hypothyroidism in a female with an estimated dose 109 mGy.

The first alternative definition added only two cases with diagnoses based on medical records without supporting documentation. Both were cases of subacute thyroiditis in women with estimated doses of 70 and 50 mGy.

For both the primary and first alternative definition of other thyroid disease, there were too few cases for meaningful estimation of the radiation dose-response.

The second alternative definition added 20 participants, primarily with participant or CATI respondent reports of past thyroid disease of unknown type. This brought the total number of cases to 26, of whom four were out-of-area participants. The number of cases and proportions with other thyroid disease are shown by sex and dose category in Table IX.N-1.

Table IX.N-1. Diagnoses of Other Thyroid Disease by Sex, Dose Category, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose	Living Evaluable Female	Primary Definition: Cases Based on HTDS Examination or Medical Records with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS Examination or Medical Records with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%	No.	%
Out of Area	125	0	--	0	--	1	0.8
< 10	182	0	--	0	--	1	0.5
10-49	320	0	--	0	--	1	0.3
50-99	313	0	--	2	0.6	5	1.6
100-149	220	1	0.5	1	0.5	2	0.9
150-199	126	0	--	0	--	1	0.8
200-299	139	0	--	0	--	2	1.4
300-399	144	2	1.4	2	1.4	2	1.4
400-999	171	0	--	0	--	2	1.2
1000+	7	0	--	0	--	0	--
Total	1747	3	0.2	5	0.3	17	1.0

B. Male

Thyroid Radiation Dose	Living Evaluable Male	Primary Definition: Cases Based on HTDS Examination or Medical Records with Supporting Documentation		1st Alternative Definition: Cases Based on HTDS Examination or Medical Records with or without Supporting Documentation		2nd Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
(mGy)	No.	No.	%	No.	%	No.	%
Out of Area	124	0	--	0	--	3	2.4
< 10	186	0	--	0	--	1	0.5
10-49	314	0	--	0	--	0	--
50-99	310	0	--	0	--	2	0.6
100-149	171	1	0.6	1	0.6	1	0.6
150-199	109	0	--	0	--	0	--
200-299	148	0	--	0	--	1	0.7
300-399	160	0	--	0	--	0	--
400-999	154	0	--	0	--	1	0.6
1000+	17	0	--	0	--	0	--
Total	1693	1	0.1	1	0.1	9	0.5

Parameter estimates for the linear dose-response model based on the 3191 in-area participants, and using the second alternative definition of other thyroid disease, are shown in Table IX.N-2 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, the estimated slope B was slightly greater than zero (0.002 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.002 to 0.024 per Gy, providing no evidence that cumulative incidence increased significantly with increasing dose (one-tailed $p = 0.39$). The corresponding estimated background rates for diagnosis of other thyroid disease were 0.010 with confidence interval (0.003, 0.016) for women and 0.003 with confidence interval (0, 0.008) for men.

Table IX.N-2. Dose-Response Results for Diagnoses of Other Thyroid Disease

Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
	Female	Male		
Alternative Definition 2: Maximum Likelihood (Any diagnosis or participant/respondent report)	.010 ± .003 (.003, .016)	.003 ± .002 (0*, .008)	.002 ± .007 (< –.002, .024)	0.39

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses. ("<" indicates that the lower confidence limit is less than the indicated value). "0*" indicates that the lower confidence limit for a background rate was less than 0.

In view of the small number of cases, and their heterogeneous and mostly unknown diagnoses, further analyses of this outcome were not performed.

O. Hyperparathyroidism

O.1. Occurrence of Hyperparathyroidism

The primary and alternative definitions of hyperparathyroidism were as follows:

- Primary definition: HTDS evaluation or medical records with supporting documentation (12 cases)
- Alternative definition #1: Any diagnosis or participant/respondent report (14 cases).

Fourteen (0.4%) living evaluable participants had diagnoses of hyperparathyroidism (Table IX.O-1), with 11 being based on the HTDS evaluation, 1 on medical records with supporting documentation, and 2 on a participant or his/her CATI respondent report.

One additional living evaluable participant who did not meet the study's criteria for hyperparathyroidism nevertheless had an elevated calcium in the presence of a high normal PTH level, when the PTH should have been suppressed, highly suggestive of hyperparathyroidism. This participant was included as a case in an additional analysis.

Table IX.O-1. Basis for Diagnosis of Hyperparathyroidism, by Sex

	Female		Male		Total	
Basis for Diagnosis	No.	%	No.	%	No.	%
Yes	10	0.6	4	0.2	14	0.4
▪ HTDS evaluation	9	0.5	2	0.1	11	0.3
▪ Medical records with supporting documentation	1	0.1	0	--	1	0.0
▪ Participant/respondent report	0	--	2	0.1	2	0.1
No	1729	99.0	1687	99.6	3416	99.3
Unknown	8	0.5	2	0.1	10	0.3
Total	1747	100.0	1693	100.0	3440	100.0

Ten living evaluable participants were classified as "unknown" with regard to diagnosis of hyperparathyroidism. These 10 did not have medical record or participant/respondent reports of such diagnoses, and did not have an HTDS evaluation due to the lack of a blood draw (8) or a sufficient amount of blood drawn to determine the serum calcium level (2). These 10 participants were included as non-cases in analyses of the dose-response for hyperparathyroidism.

O.2. Analysis of Hyperparathyroidism Risk

O.2.a. Primary Analysis

Of the 12 living evaluable participants with a diagnosis of hyperparathyroidism based on the HTDS examination or medical records with supporting documentation, one was an out-of-area participant for whom the CIDER program could not calculate a dose estimate. The proportions with hyperparathyroidism are shown by sex, dose category and basis for diagnosis in Table IX.O-2.

Table IX.O-2. Diagnoses of Hyperparathyroidism by Sex, Estimated Dose, and Basis for Diagnosis

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%
Out of Area	125	0	--	0	--
< 10	182	1	0.5	1	0.5
10-49	320	2	0.6	2	0.6
50-99	313	2	0.6	2	0.6
100-149	220	1	0.5	1	0.5
150-199	126	1	0.8	1	0.8
200-299	139	2	1.4	2	1.4
300-399	144	1	0.7	1	0.7
400-999	171	0	--	0	--
1000+	7	0	--	0	--
Total	1747	10	0.6	10	0.6

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male	Primary Definition: Cases Based on HTDS or Med. Rec. with Supporting Documentation		Alternative Definition: Cases Based on Any Diagnosis or Participant or CATI Report	
	No.	No.	%	No.	%
Out of Area	124	1	0.8	1	0.8
< 10	186	0	--	0	--
10-49	314	0	--	0	--
50-99	310	0	--	1	0.3
100-149	171	1	0.6	1	0.6
150-199	109	0	--	0	--
200-299	148	0	--	0	--
300-399	160	0	--	0	--
400-999	154	0	--	1	0.6
1000+	17	0	--	0	--
Total	1693	2	0.1	4	0.2

Parameter estimates for the linear dose-response model based on the 3191 in-area participants are shown in Table IX.O-3 below. Based on maximum likelihood analysis of the sex-stratified linear probability model, and using the primary dose estimates, the estimated slope B was –0.000 per Gy (row 1 of Table IX.O-3). The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.013 per Gy, and the cumulative incidence of hyperparathyroidism did not increase significantly with increasing dose ($p = 0.61$). The corresponding estimated background rates for diagnosis of hyperparathyroidism were 0.006 with confidence interval (0, 0.013) for women and 0.001 with confidence interval (0, 0.006) for men. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was slightly more negative than the maximum likelihood estimate (Table IX.O-3, rows 2 and 3), thereby providing no evidence that risk of hyperparathyroidism increased with increasing dose ($p = 0.74$ and 0.75).

Table IX.O-3. Summary of Dose-Response Results for Diagnoses of Hyperparathyroidism

Row	Outcome	Dose Response Model	Dose Estimates	Exclusion: Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition (HTDS evaluation)	Linear	Primary	None	MLE	.006 ± .003 (0*, .013)	.001 ± .002 (0*, .006)	–.000 ± .018 (NE, .013)	0.61
2.	Primary definition	Linear	Primary	None	LSU	.007 ± .002 (.003, .011)	.001 ± .002 (0*, .005)	–.003 ± .005 (–.014, .008)	0.74
3.	Primary definition	Linear	Primary	None	LSG	.007 ± .002 (.003, .011)	.001 ± .002 (0*, .006)	–.004 ± .005 (–.016, .009)	0.75
4.	Alternative def. #1 (Any diagnosis or participant/respondent report)	Linear	Primary	None	MLE	.006 ± .002 (.001, .011)	.002 ± .002 (0*, .006)	.000 ± .006 (< –.001, .021)	0.47
5.	Hyperparathyroidism plus probable case	Linear	Primary	None	MLE	.006 ± .002 (.001, .011)	.003 ± .002 (0*, .008)	–.001 ± .007 (< –.001, .023)	0.54

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.O-3. Summary of Dose-Response Results for Diagnoses of Hyperparathyroidism (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates Female	Estimated Background Rates Male	Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
6.	Primary definition	LQ	Primary	None	LSU	.007 ± .002 (.002, .011)	.001 ± .002 (0*, .006)	Lin: –.003 ± .008 (–.023, .017) Quad: .000 ± .005 (–.013, .013)	Quad: 0.99
7.	Primary definition	Logistic	Primary	None	MLE	.008 (.003, .020)	.001 (.0001, .009)	–1.34 ± 2.00 (-6.14, 3.46)	0.77
8.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.006 ± .003 (0*, .014)	.001 ± .002 (0*, .006)	-.001 ± .018 (NE, .014)	0.67
9.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.006 ± .003 (0*, .014)	.000 ± .003 (0*, .006)	.006 ± .022 (<.000, .031)	0.31
10.	Primary definition	Linear	Primary	Exclude Ok and F/S geostrata	MLE	.006 ± .003 (0*, .014)	.001 ± .002 (0*, .006)	-.0003 ± .018 (NE, .013)	0.62
11.	Primary definition	Linear	Alt. #1	None	MLE	.006 ± .003 (0*, .013)	.000 ± .005 (0*, .012)	-.0002 ± .018 (<-.0003, .013)	0.42

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.O-3. Summary of Dose-Response Results for Diagnoses of Hyperparathyroidism

Row	Outcome	Dose Response Model	Dose Estimates	Exclusion: Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #2	None	MLE	.006 ± .003 (0*, .013)	.001 ± .001 (0*, .004)	-.0003 ± .011 (NE, .013)	0.60
13.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.006 ± .002 (.0002, .011)	.001 ± .001 (0*, .004)	-.0005 ± .011 (NE, .011)	0.68
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.006 ± .002 (.000, .011)	.001 ± .001 (0*, .004)	-.0005 ± .011 (NE, >.010)	0.68

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model. "0*" indicates that the lower confidence limit for a background rate was less than 0.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

O.2.b. Alternative Definitions for Diagnosis of Hyperparathyroidism

One alternative definition for cases of hyperparathyroidism was considered. This alternative added two cases based solely on reports from the participant or his/her CATI respondent, bringing the total to 14 cases. The two added cases had estimated doses of 475 and 92 mGy. As shown in row 4 of Table IX.O-3 above, in the alternative analysis the cumulative incidence of hyperparathyroidism did not increase significantly with increasing dose (p = 0.47), with an estimated slope of 0.000 per Gy and Bonferroni-adjusted 95% confidence interval ranging from less than –0.001 to 0.021 per Gy.

O.2.b.1 Effect of Including Probable Diagnoses of Hyperparathyroidism

As described in IX.O.1 above, one living evaluable participant who wasn't counted as a case of hyperparathyroidism might truly have been a case. This participant was not counted as a case in the primary analysis of hyperparathyroidism to avoid introducing a possible reporting bias. However in view of the importance of hyperparathyroidism as a disease outcome, an additional analysis in which this participant was counted as a case was performed. This participant was in the in-area group, with an estimated thyroid radiation dose of 159 mGy. Counting this participant as a case rather than a noncase in the dose-response analysis had almost no impact on the results (Table IX.O-3, row 5): the estimated slope of the dose-response was slightly less than zero (–0.001 per Gy, with confidence interval ranging from less than –0.001 to 0.023 per Gy) providing no evidence of a positive dose-response (p=0.54).

O.2.c. Alternative Dose-Response Functions

As shown in row 6 of Table IX.O-3, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.000 with Bonferroni-adjusted 95% confidence interval ranging from –0.013 to 0.013. Thus the addition of a quadratic term did not significantly improve the fit of the model (p = 0.99).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –1.34, with Bonferroni-adjusted 95% confidence limits –6.14 and 3.46, indicating that the cumulative evidence of hyperparathyroidism did not increase significantly with increasing dose (p = 0.77; see row 7 of Table IX.O-3).

O.2.d. Effect of Excluding Participants in High Dose Categories

As shown in rows 8 and 9 of Table IX.O-3, when participants in high dose categories were excluded, the cumulative incidence of hyperparathyroidism did not increase significantly with increasing dose (p = 0.67 and p = 0.31 when those with doses >1000 mGy and >400 mGy were excluded, respectively).

O.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

When participants in the Okanogan and Ferry/Stevens were excluded, the estimated slope B was slightly less than zero (-0.0003 with Bonferroni-adjusted 95% CI upper confidence limit of 0.013), providing no evidence that the cumulative incidence of hyperparathyroidism increased with increasing dose (p = 0.62; Table IX.O-3, row 10).

O.2.f. Analysis of Hyperparathyroidism in Relation to Alternative Dose Estimates

As shown in rows 11 and 12 of Table IX.O-3 above, for neither set of alternative dose estimates did the cumulative incidence of hyperparathyroidism increase significantly with increasing dose ($p = 0.42$ and 0.60 for dose alternatives 1 and 2, respectively).

O.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of including the 249 out-of-area participants. As shown in rows 13 and 14 of Table IX.O-3, the results of both scoping analyses were very similar to those of the primary analysis (row 1). In particular, neither scoping analysis provided evidence that the risk of hyperparathyroidism increased with increased thyroid dose ($p = 0.68$ for both scoping analyses).

O.2.h. Analysis of Hyperparathyroidism in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of cumulative incidence were performed as described in section VIII.C.2.a.2.

O.2.h.1. Analysis by Geostratum

Since there were only 12 participants with hyperparathyroidism diagnosed according to the primary definition (HTDS or medical records with documentation), the test for heterogeneity among the 9 geostrata had little statistical power. Therefore the absence of significant heterogeneity ($p = 0.71$) was not strong evidence against the possibility that the cumulative incidence of hyperparathyroidism might in fact vary among the geostrata.

Table IX.O-4. Diagnoses of Hyperparathyroidism Based on the HTDS Evaluation or on Medical Records with Supporting Documentation, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	179	0	--	173	0	--	352	0	--
Pasco/Kennewick	508	4	0.8	501	1	0.2	1009	5	0.5
Benton County	376	3	0.8	358	0	--	734	3	0.4
Franklin County	73	0	--	76	0	--	149	0	--
Adams County	165	0	--	156	1	0.6	321	1	0.3
Walla Walla (city)	133	1	0.8	131	0	--	264	1	0.4
Walla Walla County	170	1	0.6	164	0	--	334	1	0.3
Okanogan County	75	0	--	64	0	--	139	0	--
Ferry/Stevens Counties	68	1	1.5	70	0	--	138	1	0.7
Total	1747	10	0.6	1693	2	0.1	3440	12	0.3

O.2.h.2. Analysis by Dichotomous Exposure Variable

See section VIII.B.3.b.2 above for a description of the high and low exposure categories. Only six (0.5%) of the 1257 participants included in these analyses had a diagnosis of hyperparathyroidism based on the HTDS examination. Therefore the comparison between the high and low exposure groups was based on the alternative definition for diagnoses of hyperparathyroidism (section IX.O.1 above), i.e., any diagnosis based on the HTDS examination, medical records, or participant or CATI respondent report. As shown in Table IX.O-5 below, using the alternative criterion increased the number of cases to only seven (0.6%). Four of these cases occurred among the 580 participants in the high exposure category (0.7%), compared to three (0.4%) among 677 participants in the low exposure group. Consequently the cumulative incidence of hyperparathyroidism was not significantly elevated in the high exposure group (p = 0.43).

Table IX.O-5. Diagnoses of Hyperparathyroidism Based on HTDS Any Diagnosis or Participant/CATI Respondent Report, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	351	2	0.6	326	1	0.3	677	3	0.4
High	298	2	0.7	282	2	0.7	580	4	0.7
Total	649	4	0.6	608	3	0.5	1257	7	0.6

O.2.i. Confounding and Effect Modification

There were too few participants with diagnoses of hyperparathyroidism to permit meaningful analysis of confounding or effect modification.

O.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for hyperparathyroidism are shown in Figure IX.O-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. The point estimate of the slope was greater than zero for 51 of the 100 realizations, and the confidence interval included zero for 97 of the 100 realizations. Also shown in Figure IX.O-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for only three of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for about half of the realizations the estimated slope was less than 0.

Figure IX.O-1. Plot of Estimated Slope and 95% CI by Dose Realization: Hyperparathyroidism

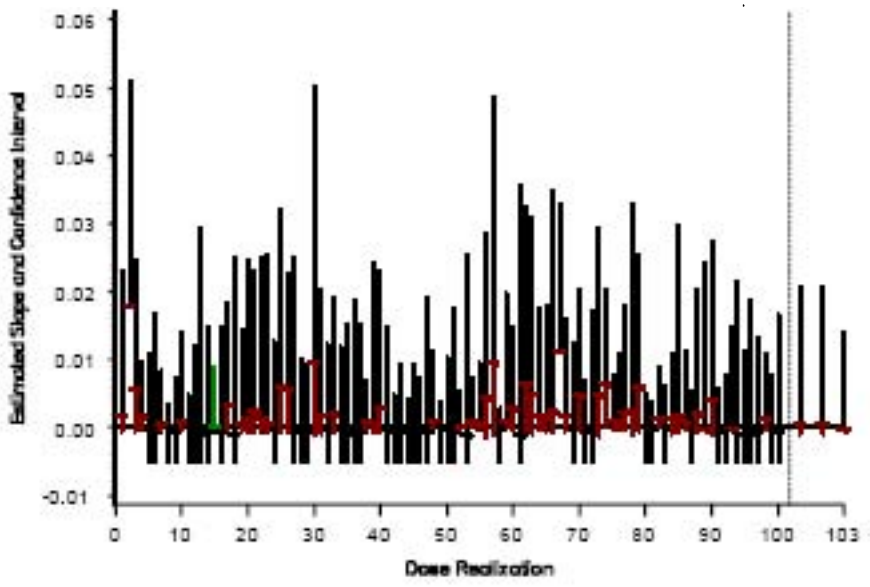
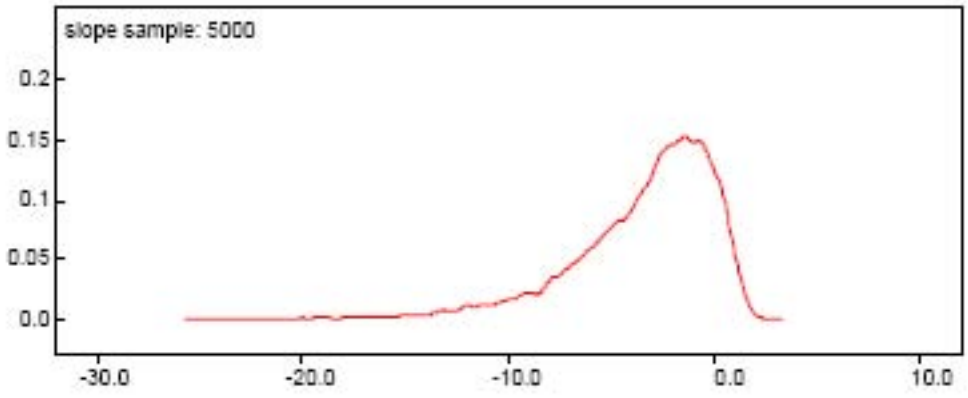


Figure IX.O-2 displays the distribution of the 5000 estimates of the logistic regression coefficient obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –15.0 and 2.0. The estimate was less than or equal to 0 for 4378 of the 5000 replications, implying an empirical one-tailed p-value of 0.88. The median estimate was –2.56, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval ranging from –15.9 to 1.42. These may be compared to the estimate of –1.34 with confidence interval (–6.14, 3.46) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the cumulative incidence of hyperparathyroidism increased with increasing dose.

Figure IX.O-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Hyperparathyroidism



P. Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

P.1. Occurrence of Ultrasound-Detected Abnormalities of the Thyroid

The thyroid gland was visible in the ultrasound examinations of 3429 of the 3440 living evaluable participants. For 11 participants the thyroid was not visible, 10 because of thyroid surgery and one because the sonographer couldn't adequately visualize the thyroid. Among the 3429 whose thyroids were visible, 1596 (46.5%) had one or more ultrasound-detected abnormalities (Table IX.P-1), including palpable thyroid UDAs (224 or 6.5%), nonpalpable focal thyroid UDAs (1309 or 38.2%), and diffuse thyroid UDAs (458 or 13.4%). All three types of thyroid UDA were more frequent among women than men. Ultrasound-detected thyroid abnormalities were based only on the HTDS evaluation, not on any prior ultrasounds.

Table IX.P-1. Ultrasound-Detected Abnormalities, by Sex and Type of Abnormality

	Female		Male		Total	
Ultrasound Finding	No.	%	No.	%	No.	%
Thyroid gland visible on ultrasound	1738	100.0	1691	100.0	3429	100.0
Normal ultrasound	774	44.5	1059	62.6	1833	53.5
Any abnormality	964	55.5	632	37.4	1596	46.5
Palpable thyroid UDAs	154	8.9	70	4.1	224	6.5
Nonpalpable focal thyroid UDAs	784	45.1	525	31.0	1309	38.2
Diffuse thyroid UDAs	306	17.6	152	9.0	458	13.4

Note: a participant can have more than one of palpable, nonpalpable focal and diffuse thyroid UDAs.

P.1.a. Additional Outcomes Related to Ultrasound-Detected Abnormalities of the Thyroid

P.1.a.1 Thyroid UDAs by Size

To determine whether the size of thyroid UDAs detected increased in relation to estimated dose, three additional outcomes were defined. These included the presence of a focal thyroid UDA with maximum dimension at least 5 mm, the presence of a focal thyroid UDA with maximum dimension of at least 10 mm, and the presence of a focal thyroid UDA with average dimension of at least 15 mm. Among the 3429 participants whose thyroids were visible, 1142 (33.3%) had a focal thyroid UDA with maximum dimension ≥ 5 mm, 622 (18.1%) had a focal thyroid UDA with maximum dimension ≥ 10 mm, and 166 (4.8%) had a focal thyroid UDA with average dimension ≥ 15 mm (Table IX.P-2).

Table IX.P-2. Ultrasound-Detected Abnormalities, by Sex and Size of Abnormality

	Female		Male		Total	
Ultrasound Findings	No.	%	No.	%	No.	%
Thyroid gland visible on ultrasound	1738	100.0	1691	100.0	3429	100.0
UDA ≥ 5 mm maximum dimension	701	40.3	441	26.1	1142	33.3
UDA ≥ 10 mm maximum dimension	390	22.4	232	13.7	622	18.1
UDA ≥ 15 mm average dimension	105	6.0	61	3.6	166	4.8

P.2. Analysis of Any Ultrasound-Detected Abnormality Risk

P.2.a. Primary Analysis

Among the 3429 participants whose thyroids were visible on ultrasound, 1596 (46.5%) had some type of ultrasound-detected abnormality. These included 3181 in-area participants, of whom 1481 (46.6%)

had any thyroid UDAs, and 248 out of area participants, of whom 115 (46.4%) had thyroid UDAs. The proportions with any thyroid UDA are shown by sex and dose category in Table IX.P-3. The prevalence of thyroid UDAs was higher among women (55.5%) compared to men (37.4%). The numbers and proportions of cases of additional outcomes related to UDAs are also shown in Table IX.P-3.

Table IX.P-3. Any Ultrasound-Detected Abnormality by Sex and Dose Category

A. Female

Thyroid Radiation Dose	L.E. with Ultrasound	Any Thyroid UDA		Focal Thyroid UDA with Maximum Dimension ≥ 5mm		Focal Thyroid UDAs with Maximum Dimension ≥ 10 mm		Focal Thyroid UDAs with Average Dimension ≥ 15 mm	
(mGy)	No.	No.	%	No.	%	No.	%	No.	%
Out of Area	124	64	51.6	50	40.3	26	21.0	4	3.2
< 10	182	100	54.9	73	40.1	43	23.6	10	5.5
10-49	318	171	53.8	126	39.6	73	23.0	16	5.0
50-99	311	172	55.3	118	37.9	65	20.9	16	5.1
100-149	220	131	59.5	97	44.1	53	24.1	13	5.9
150-199	125	65	52.0	49	39.2	32	25.6	14	11.2
200-299	137	79	57.7	59	43.1	26	19.0	6	4.4
300-399	143	80	55.9	55	38.5	26	18.2	11	7.7
400-999	171	100	58.5	73	42.7	46	26.9	15	8.8
1000+	7	2	28.6	1	14.3	0	--	0	--
Total	1738	964	55.5	701	40.3	390	22.4	105	6.0

L.E. = living evaluable participants

B. Male

Thyroid Radiation Dose	L.E. with Ultrasound	Any Thyroid UDA		Focal Thyroid UDA with Maximum Dimension ≥ 5mm		Focal Thyroid UDA with Maximum Dimension ≥ 10 mm		Focal Thyroid UDA with Average Dimension ≥ 15 mm	
(mGy)	No.	No.	%	No.	%	No.	%	No.	%
Out of Area	124	51	41.1	39	31.5	17	13.7	2	1.6
< 10	185	72	38.9	52	28.1	29	15.7	9	4.9
10-49	314	111	35.4	78	24.8	47	15.0	14	4.5
50-99	310	103	33.2	72	23.2	40	12.9	12	3.9
100-149	171	64	37.4	40	23.4	23	13.5	4	2.3
150-199	109	46	42.2	34	31.2	16	14.7	5	4.6
200-299	148	66	44.6	53	35.8	29	19.6	9	6.1
300-399	160	65	40.6	40	25.0	18	11.3	4	2.5
400-999	153	44	28.8	27	17.6	10	6.5	1	0.7
1000+	17	10	58.8	6	35.3	3	17.6	1	5.9
Total	1691	632	37.4	441	26.1	232	13.7	61	3.6

L.E. = living evaluable participants

Parameter estimates for the linear dose-response model based on the 3181 in-area participants with ultrasound results are shown in Table IX.P-4. Based on maximum likelihood analysis of the sex-stratified linear probability model, the risk of having any type of thyroid UDA did not increase significantly with

estimated dose (p = 0.21), with an estimated slope B of 0.031 per Gy, and 95% CI ranging from –0.059 to 0.116 per Gy (Table IX.P-4, row 1). Estimation by least squares using the ungrouped data gave nearly identical results, and the least squares fit to the grouped data were similar (Table IX.P-4, rows 2 and 3).

Table IX.P-4. Dose-Response Results for Diagnoses of Any Thyroid UDA

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition	Linear	Primary	None	MLE	.552 ± .014 (.519, .586)	.365 ± .014 (.332, .399)	.031 ± .038 (–.059, .116)	0.21
2.	Primary definition	Linear	Primary	None	LSU	.552 ± .014 (.519, .585)	.365 ± .014 (.331, .399)	.032 ± .039 (–.061, .125)	0.21
3.	Primary definition	Linear	Primary	None	LSG	.556 ± .014 (.522, .591)	.369 ± .015 (.334, .405)	.008 ± .045 (–.099, .115)	0.43
4.	Focal thyroid UDA with max dimension ≥ 5 mm	Linear	Primary	None	MLE	.406 ± .014 (.373, .438)	.259 ± .013 (.228, .290)	-.013 ± .037 (-.097, .077)	0.64
5.	Focal thyroid UDA with max dimension ≥ 10 mm	Linear	Primary	None	MLE	.231 ± .011 (.204, .258)	.143 ± .010 (.119, .167)	-.033 ± .026 (<-.061, .038)	0.88

Entries in the tables are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.P-4. Dose-Response Results for Diagnoses of Any Thyroid UDA (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
6.	Focal thyroid UDA with average dimension ≥ 15 mm	Linear	Primary	None	MLE	.063 ± .007 (.047, .079)	0.038 ± .005 (.025, .051)	-.001 ± .015 (<-.017, .044)	0.53
7.	Primary definition	LQ	Primary	None	LSU	.546 ± .015 (.509, .584)	.359 ± .015 (.321, .397)	Lin: .086 ± .067 (–.078, .250) Quad: –.045 ± .044 (–.153, .064)	Quad: 0.30
8.	Primary definition	Logistic	Primary	None	MLE	.552 (.518, .586)	.365 (.333, .399)	.133 ± .162 (–.254, .520)	0.21
9.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.552 ± .015 (.517, .587)	.362 ± .015 (.327, .397)	.042 ± .049 (<–.075, >.159)	0.20
10.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.535 ± .016 (.496, .575)	.356 ± .016 (.317, .395)	.179 ± .086 (–.027, .384)	0.019
11.	Primary definition	Linear	Primary	Exclude OK and F/S geostrata	MLE	.547 ± .015 (.512, .583)	.353 ± .015 (.318, .387)	.047 ± .038 (–.045, .130)	0.11

Entries in the tables are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.P-4. Dose-Response Results for Diagnoses of Any Thyroid UDA (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
12.	Primary definition	Linear	Alt. #1	None	MLE	.556 ± .014 (.521, .590)	.369 ± .014 (.335, .403)	.009 ± .038 (–.080, .097)	0.40
13.	Primary definition	Linear	Alt. #2	None	MLE	.555 ± .014 (.521, .590)	.368 ± .014 (.335, .402)	.012 ± .038 (–.078, .103)	0.37
14.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.549 ± .013 (.518, .581)	.368 ± .013 (.337, .400)	.033 ± .037 (<-.056, .017)	0.19
15.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.550 ± .013 (.518, .582)	.369 ± .013 (.338, .401)	.027 ± .037 (–.062, .112)	0.24

Entries in the tables are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

P.2.b. Effect of Using Alternative Size Criteria for Thyroid UDAs

To assess whether the dose-response results might be affected by the size of focal thyroid UDAs, three additional outcomes were analyzed. These included the presence of a focal thyroid UDA with maximum dimension at least 5 mm, the presence of a focal thyroid UDA with maximum dimension at least 10 mm, and the presence of a focal thyroid UDA with average dimension at least 15 mm. These additional analyses applied only to palpable and nonpalpable focal thyroid UDAs, since diffuse thyroid UDAs were not defined by any size criterion. In none of these additional analyses was there any evidence that the risk of having a focal thyroid UDA of a particular size increased with increasing dose ($p = 0.64$, 0.88 and 0.53 for the presence of focal thyroid UDA with maximum dimension of 5 mm, maximum dimension of 10 mm and average dimension of 15 mm, respectively; Table IX.P-4, rows 4, 5, and 6).

P.2.c. Alternative Dose-Response Functions

As shown in row 7 of Table IX.P-4, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was –0.045 with Bonferroni-adjusted 95% confidence interval ranging from –0.153 to 0.064. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.30$).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.133, with Bonferroni-adjusted 95% confidence limits –0.254 and 0.520, indicating that the prevalence of any thyroid UDA did not increase significantly with increasing dose ($p = 0.21$; Table IX.P-4, row 8).

P.2.d. Effect of Excluding Participants in High Dose Categories

In the analyses excluding participants with estimated dose > 1000 mGy (Table IX.P-4, row 9), the estimated slope B was not significantly greater than zero (0.042 per Gy, with Bonferroni-adjusted 95% CI ranging from less than –0.075 to greater than 0.159) providing no evidence that the prevalence of any thyroid UDA increased with increasing dose ($p = 0.20$). When all participants with estimated dose > 400 mGy were excluded (Table IX.P-4, row 10), the estimated slope B was not significantly greater than zero (0.179 per Gy, with Bonferroni-adjusted 95% CI ranging from –0.027 to 0.384). Although there was some evidence that the prevalence of any thyroid UDA increased with increasing dose ($p = .019$), this finding was not considered statistically significant given the large number of such tests that were performed.

P.2.e. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

As shown in row 11 of Table IX.P-4, excluding Okanogan and Ferry/Stevens slightly reduced the estimated background rates for both men and women. The reductions are small, because the Okanogan and Ferry/Stevens geostrata account for only 255 (8.0%) of the 3181 in-area living evaluable participants with ultrasound results. As a result of these reductions in the background rates and the fact that Okanogan and Ferry/Stevens geostrata tend to have low doses, the estimated slope increased slightly, from 0.031 to 0.047, and the statistical significance of the dose-response changed from $p = 0.21$ to $p = 0.11$.

P.2.f. Analysis of Ultrasound-Detected Abnormalities in Relation to Alternative Dose Estimates

As shown in row 12 of Table IX.P-4, using the first alternative dose estimates, the estimated slope B was not significantly greater than zero (0.009 per Gy with Bonferroni-adjusted 95% CI ranging from

-0.080 to 0.097), providing no evidence that prevalence increased with increasing dose (p = 0.40; Table IX.P-4, row 12). Similar results were found with the second set of alternative dose estimates (Table IX.P-4, row 13).

P.2.g. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of the 249 out-of-area participants. The results of both scoping analyses were virtually the same as the primary analysis and provided no evidence that the prevalence of any thyroid UDA increased with increasing dose (Table IX.P-4, rows 14 and 15).

P.2.h. Analysis of Any Thyroid UDAs In Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of prevalence were performed as described in section VIII.C.2.a.2.

P.2.h.1. Analysis by Geostratum

As shown in Table IX.P-5, among the 3429 living evaluable in area or out-of-area participants with ultrasound results, the proportions with any UDAs ranged from 83/131 (63.4% in the Walla Walla City geostratum) to 92/177 (52.0%, Richland) for women, and from 32/63 (50.8%, Okanogan County) to 41/164 (25.0%, Walla Walla County) for men (p = 0.014 for heterogeneity among the nine geostrata). In particular the percentages with any UDAs were somewhat higher in the Okanogan and Ferry/Stevens geostrata (58.7% for women, 48.1% for men) than in the remaining geostrata (55.2% and 36.5%, respectively; p = 0.012). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.

Table IX.P-5. Any Ultrasound-Detected Abnormality, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	177	92	52.0	172	60	34.9	349	152	43.6
Pasco/Kennewick	505	273	54.1	501	176	35.1	1006	449	44.6
Benton County	375	206	54.9	358	146	40.8	733	352	48.0
Franklin County	73	42	57.5	76	36	47.4	149	78	52.3
Adams County	165	93	56.4	156	66	42.3	321	159	49.5
Walla Walla (city)	131	83	63.4	131	43	32.8	262	126	48.1
Walla Walla County	169	91	53.8	164	41	25.0	333	132	39.6
Okanogan County	75	43	57.3	63	32	50.8	138	75	54.3
Ferry/Stevens Counties	68	41	60.3	70	32	45.7	138	73	52.9
Total	1738	964	55.5	1691	632	37.4	3429	1596	46.5

P.2.h.2. Analysis by Dichotomous Exposure Variable

Ultrasound was not evaluable for 2 of the 1257 living evaluable participants included in these analyses. Of the 1255 participants included in these analyses, 611 (48.7%) had one or more thyroid UDAs (Table IX.P-6). These included 291/580 (50.2%) in the high exposure group, and 320/675 (47.4%) in the low exposure group. Based on the logistic regression analysis with adjustment for the effect of sex and age

at HTDS examination, the proportion of participants with any thyroid UDA was not significantly elevated in the high exposure group ($p = 0.11$).

Table IX.P-6. Any Ultrasound-Detected Abnormality, by Exposure Group and Sex

Exposure	Female			Male			Total		
Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	350	192	54.9	325	128	39.4	675	320	47.4
High	298	183	61.4	282	108	38.3	580	291	50.2
Total	648	375	57.9	607	236	38.9	1255	611	48.7

P.2.i. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results for any thyroid UDA might be influenced by confounding, and to search for factors that might modify a radiation dose-response. Table IX.P-7 displays results for models including sex, age at first exposure to Hanford I-131 (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type.

Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. None of the other factors in Table IX.P-7 appears to be a confounder: for none does the adjusted estimate of the regression coefficient differ markedly from the unadjusted estimate. Therefore, it does not appear that omitting these factors introduced any important bias in the dose-response results.

Table IX.P-7. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Any Ultrasound-Detected Abnormality

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1614 / 3181	.133 ± .162 (–.254, .520)	Not Applicable	.198 ± .226 (–.368, .763)	.067 ± .228 (–.504, .637)	.68
Prenatal exposure?	1031 / 3181	.133 ± .162 (–.254, .520)	.087 ± .163 (–.332, .506)	.190 ± .188 (–.305, .685)	–.235 ± .333 (–1.12, .644)	.26
1st exposure before age 180 days?	1474 / 3181	.133 ± .162 (–.254, .520)	.121 ± .162 (–.297, .539)	.373 ± .279 (–.362, 1.11)	–.010 ± .200 (–.538, .519)	.26
Age at exam > 50?	1993 / 3181	.133 ± .162 (–.254, .520)	.178 ± .164 (–.246, .601)	–.038 ± .297 (–.822, .746)	.271 ± .197 (–.248, .791)	.39
NTS I-131 dose > 5.3 mGy?	1563 / 3179	.127 ± .162 (–.260, .514)	.111 ± .165 (–.314, .536)	.106 ± .219 (–.471, .682)	.118 ± .251 (–.544, .781)	.97
History of any cancer other than thyroid?	248 / 3176	.138 ± .162 (–.249, .525)	.141 ± .162 (–.276, .557)	.219 ± .176 (–.244, .683)	–.300 ± .427 (–1.43, .827)	.25
Expanded In-Person Interview?	1205 / 3181	.133 ± .162 (–.254, .520)	.159 ± .165 (–.266, .584)	.277 ± .263 (–.416, .970)	.083 ± .211 (–.475, .640)	.56

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.P-8 and IX.P-9 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. Specifically, none of the factors in these tables appears to be a confounder or an effect modifier.

Table IX.P-8. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Any Ultrasound-Detected Abnormality

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification		
				Group 0	Group 1	P
CAT scan of the upper body?	775 / 3139	.130 ± .162 (–.257, .518)	.130 ± .162 (–.288, .548)	.064 ± .178 (–.406, .533)	.450 ± .391 (–.581, 1.48)	.37
Diagnostic x-rays of the head?	1188 / 3145	.133 ± .163 (–.257, .523)	.129 ± .163 (–.291, .549)	.257 ± .204 (–.280, .795)	–.110 ± .279 (–.845, .625)	.29
Diagnostic x-rays of the neck?	960 / 3157	.126 ± .162 (–.263, .515)	.129 ± .163 (–.290, .548)	.016 ± .211 (–.541, .574)	.299 ± .263 (–.394, .993)	.40
Diagnostic x-rays of chest or upper body, including mammograms?	2811 / 3163	.130 ± .162 (–.257, .518)	.141 ± .162 (–.276, .558)	.503 ± .573 (–1.01, 2.01)	.110 ± .169 (–.335, .555)	.51
Diagnostic x-rays of the stomach or mid-back?	691 / 3110	.175 ± .164 (–.218, .567)	.178 ± .164 (–.244, .601)	.141 ± .183 (–.342, .625)	.327 ± .370 (–.649, 1.30)	.65
Barium enema?	821 / 3149	.122 ± .162 (–.266, .510)	.123 ± .162 (–.295, .540)	.200 ± .189 (–.298, .698)	–.097 ± .318 (–.937, .743)	.42
Upper GI?	1140 / 3167	.126 ± .162 (–.262, .513)	.122 ± .162 (–.295, .539)	.067 ± .204 (–.471, .604)	.216 ± .267 (–.488, .921)	.66
Intravenous pyelogram?	396 / 3147	.143 ± .162 (–.246, .532)	.146 ± .163 (–.273, .565)	.090 ± .173 (–.366, .545)	.585 ± .482 (–.686, 1.86)	.33
Fluoroscopy of the upper body?	246 / 3151	.140 ± .162 (–.249, .528)	.141 ± .162 (–.278, .559)	.125 ± .169 (–.319, .570)	.335 ± .601 (–1.25, 1.92)	.74
Other nuclear scan?	216 / 3152	.132 ± .162 (–.256, .520)	.134 ± .162 (–.284, .552)	.216 ± .168 (–.228, .660)	–1.15 ± .698 (–2.99, .693)	.049
Dental x-rays that did not usually include a lead shield over the neck area?	1644 / 3181	.133 ± .162 (–.254, .520)	.131 ± .162 (–.285, .547)	.280 ± .231 (–.330, .890)	–.013 ± .227 (–.611, .585)	.36

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-9. Confounding and Effect Modification by Occupational History: Any Ultrasound-Detected Abnormality

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification		
				Group 0	Group 1	P
Any metal industry?	238 / 3181	.133 ± .162 (–.254, .520)	.130 ± .162 (–.286, .546)	.114 ± .166 (–.325, .553)	.385 ± .665 (–1.37, 2.14)	.69
Any nuclear facility?	370 / 3181	.133 ± .162 (–.254, .520)	.119 ± .163 (–.300, .539)	.063 ± .180 (–.412, .538)	.370 ± .379 (–.630, 1.37)	.46
Any othe industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3181	.133 ± .162 (–.254, .520)	.132 ± .162 (–.284, .548)	.236 ± .179 (–.237, .709)	–.345 ± .398 (–1.40, .706)	.17
Any of the above industries or occupations?	891 / 3181	.133 ± .162 (–.254, .520)	.138 ± .162 (–.280, .555)	.154 ± .200 (–.374, .683)	.106 ± .276 (–.622, .834)	.89

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-10 displays the results of analyses of possible confounding or effect modification by smoking variables. There was some evidence that the dose-response coefficient differed between participants with versus without histories of smoking cigarettes ($p = 0.034$) or any of cigarettes, cigars or pipes ($p = 0.024$). The estimated dose-response coefficients were greater than zero among nonsmokers, but negative for smokers. However the Bonferroni-adjusted 95% confidence intervals for the smokers' and nonsmokers' estimated coefficients overlapped, including the value of zero in the overlap. In view of the modest significance levels of the effect modification and the large number of comparisons performed in these analyses, these results do not provide compelling evidence of a statistically significant dose-response within the nonsmoking cohort.

Table IX.P-10. Confounding and Effect Modification by Smoking: Any Ultrasound-Detected Abnormality

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification		
				Group 0	Group 1	P
Cigarettes (unfiltered or filtered)?	1850 / 3173	.140 ± .162 (–.248, .527)	.139 ± .162 (–.278, .556)	.620 ± .281 (–.120, 1.36)	–.109 ± .200 (–.637, .420)	.034
Any of cigarettes, cigar or pipe?	1896 / 3173	.140 ± .162 (–.248, .527)	.139 ± .162 (–.278, .556)	.661 ± .285 (–.092, 1.41)	–.118 ± .199 (–.643, .407)	.024

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

P.2.j. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for the outcome of any thyroid UDA are shown in Figure IX.P-1 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 87 of the 100 realizations, the confidence interval includes 0 for all but 1 of the realizations. Also shown in Figure IX.P-1 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for only one of the 100 realizations of the estimated doses was there a statistically significant dose-response, although for most of the realizations the estimated slope was greater than 0.

Figure IX.P-1. Plot of Estimated Slope and 95% CI by Dose Realization: Any Ultrasound-Detected Abnormality

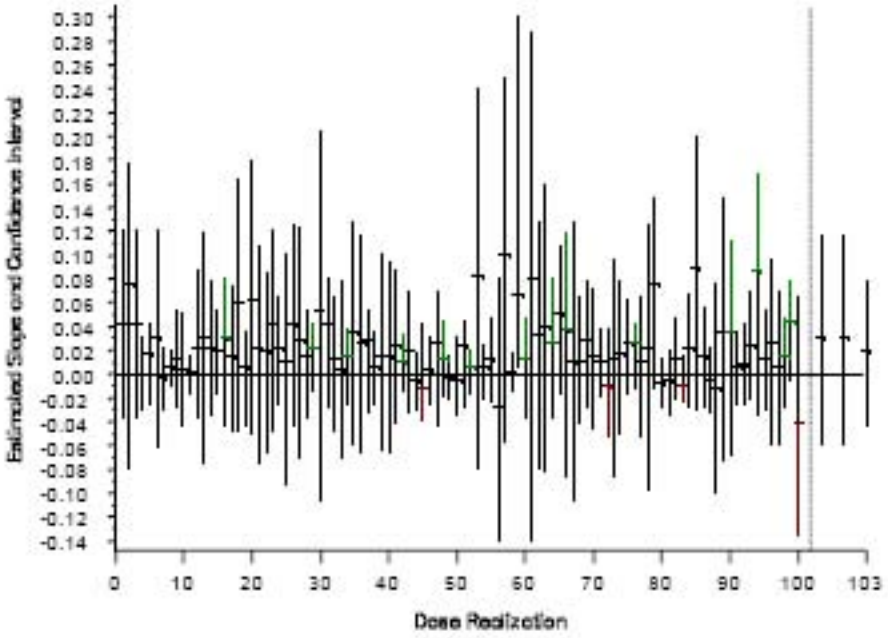
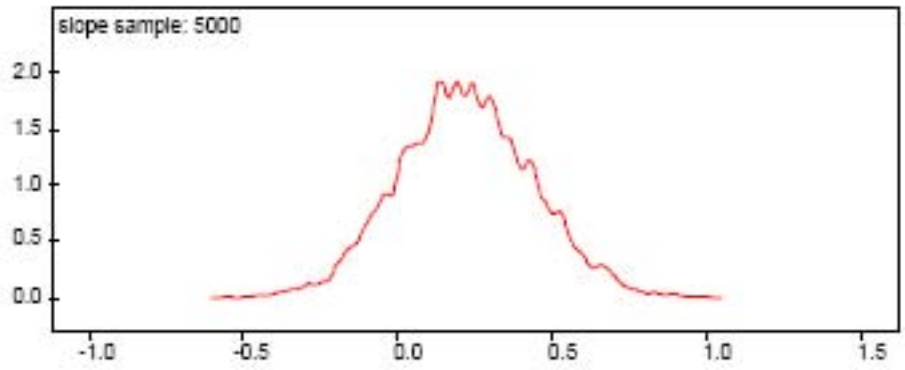


Figure IX.P-2 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –0.5 and 1.0. The estimate was less than or equal to 0 for 759 of the 5000 replications, implying an empirical one-tailed p-value of 0.15. The median estimate was 0.22, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –0.29 and 0.74. These may be compared to the p-value of 0.21 and the estimate of 0.13 with confidence internal (–0.25, 0.52) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the prevalence of any thyroid UDA increased significantly with increasing dose.

Figure IX.P-2. Distribution of Simulation Estimates of Logistic Regression Coefficient: Any Ultrasound-Detected Abnormality



P.2.k. Analyses of Numbers of Thyroid UDAs

In the analyses described above, participants were classified according to whether they did or did not have any thyroid UDAs. Additional analyses were performed to investigate whether the number of thyroid UDAs detected in individual participants might increase in relation to estimated thyroid radiation dose. For each living evaluable participant with an HTDS ultrasound examination, the numbers of focal thyroid UDAs with maximum dimension ≥ 5 mm, maximum dimension ≥ 10 mm, and average dimension ≥ 15 mm were counted. These numbers of thyroid UDAs are summarized in Tables IX.P-11 through IX.P-13 below. As shown in Table IX.P-11, study participants had as many as nine thyroid UDAs with maximum dimension ≥ 5 mm, although the majority (60% of the women and 74% of the men) had no such thyroid UDAs. The overall average number of thyroid UDAs of this size was 0.84 per person for women, and 0.47 per person for men.

Table IX.P-11. Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 5 mm, by Sex and Dose Category

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 5 mm										
		Avg.	0	1	2	3	4	5	6	7	8	9
OOA*	124	0.94	74 59.7%	26 21.0%	9 7.3%	6 4.8%	2 1.6%	2 1.6%	1 0.8%	2 1.6%	1 0.8%	1 0.8%
< 10	182	0.82	109 59.9%	40 22.0%	13 7.1%	9 4.9%	5 2.7%	2 1.1%	2 1.1%	2 1.1%	0	0
10-49	318	0.83	192 60.4%	66 20.8%	22 6.9%	15 4.7%	13 4.1%	4 1.3%	5 1.6%	1 0.3%	0	0
50-99	311	0.81	193 62.1%	59 19.0%	26 8.4%	15 4.8%	6 1.9%	4 1.3%	6 1.9%	1 0.3%	1 0.3%	0
100-149	220	0.89	123 55.9%	55 25.0%	19 8.6%	8 3.6%	9 4.1%	2 0.9%	0	1 0.5%	2 0.9%	1 0.5%
150-199	125	0.83	76 60.8%	27 21.6%	9 7.2%	2 1.6%	6 4.8%	2 1.6%	2 1.6%	1 0.8%	0	0
200-299	137	0.86	78 56.9%	29 21.2%	17 12.4%	5 3.6%	4 2.9%	1 0.7%	2 1.5%	1 0.7%	0	0
300-399	143	0.81	88 61.5%	30 21.0%	9 6.3%	10 7.0%	1 0.7%	1 0.7%	1 0.7%	1 0.7%	2 1.4%	0
400-999	171	0.82	98 57.3%	38 22.2%	19 11.1%	8 4.7%	5 2.9%	1 0.6%	1 0.6%	0	0	1 0.6%
1000+	7	0.14	6 85.7%	1 14.3%	0	0	0	0	0	0	0	0
Total	1738	0.84	1037 59.7%	371 21.4%	143 8.2%	78 4.5%	51 2.9%	19 1.1%	20 1.2%	10 0.6%	6 0.4%	3 0.2%

*OOA = Out of Area

Table IX.P-11. Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 5 mm, by Sex and Dose Category (continued)

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 5 mm										
		Avg.	0	1	2	3	4	5	6	7	8	9
OOA	124	0.56	85 68.6%	22 17.7%	11 8.9%	3 2.4%	1 0.8%	0	1 0.8%	1 0.8%	0	0
< 10	185	0.49	133 71.9%	30 16.2%	12 6.5%	3 1.6%	7 3.8%	0	0	0	0	0
10-49	314	0.44	236 75.2%	50 15.9%	13 4.1%	5 1.6%	6 1.9%	3 1.0%	0	0	0	1 0.3%
50-99	310	0.42	238 76.8%	46 14.8%	12 3.9%	6 1.9%	3 1.0%	1 0.3%	3 1.0%	0	1 0.3%	0
100-149	171	0.42	131 76.6%	25 14.6%	8 4.7%	1 0.6%	3 1.8%	3 1.8%	0	0	0	0
150-199	109	0.53	75 68.8%	21 19.3%	5 4.6%	6 5.5%	1 0.9%	1 0.9%	0	0	0	0
200-299	148	0.72	95 64.2%	30 20.3%	14 9.5%	2 1.4%	2 1.4%	0	3 2.0%	1 0.7%	0	1 0.7%
300-399	160	0.47	120 75.0%	25 15.6%	6 3.8%	4 2.5%	2 1.3%	1 0.6%	1 0.6%	1 0.6%	0	0
400-999	153	0.22	126 82.4%	22 14.4%	4 2.6%	0	1 0.7%	0	0	0	0	0
1000+	17	0.82	11 64.7%	3 17.7%	1 5.9%	1 5.9%	0	0	1 5.9%	0	0	0
Total	1691	0.47	1250 73.9%	274 16.2%	86 5.1%	31 1.8%	26 1.5%	9 0.5%	9 0.5%	3 0.2%	1 0.1%	2 0.1%

*OOA = Out of Area

Focal thyroid UDAs of larger sizes were necessarily less frequent. As shown in Table IX.P-12, participants had as many as eight focal thyroid UDAs with maximum dimension ≥ 10 mm. Again, the majority (78% of women and 86% of men) had no such thyroid UDAs, and the overall average number of thyroid UDAs of this size was 0.34 for women and 0.19 for men.

Table IX.P-12. Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 10 mm, by Sex and Dose Category

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 10 mm								
		Avg.	0	1	2	3	4	5	6	8
OOA	124	0.34	98 79.0%	17 13.7%	6 4.8%	0	2 1.6%	1 0.8%	0	0
< 10	182	0.36	139 76.4%	29 15.9%	8 4.4%	4 2.2%	2 1.1%	0	0	0
10-49	318	0.33	245 77.0%	51 16.0%	14 4.4%	6 1.9%	2 0.6%	0	0	0
50-99	311	0.30	246 79.1%	48 15.4%	12 3.9%	2 0.6%	1 0.3%	2 0.6%	0	0
100-149	220	0.40	167 75.9%	33 15.0%	13 5.9%	4 1.8%	2 0.9%	0	0	1 0.5%
150-199	125	0.42	93 74.4%	22 17.6%	5 4.0%	1 0.80	3 2.4%	1 0.8%	0	0
200-299	137	0.26	111 81.0%	20 14.6%	4 2.9%	1 0.7%	1 0.7%	0	0	0
300-399	143	0.31	117 81.8%	15 10.5%	9 6.3%	0	1 0.7%	0	0	1 0.7%
400-999	171	0.43	125 73.1%	30 17.5%	11 6.4%	1 0.6%	2 1.2%	1 0.6%	1 0.6%	0
1000+	7	0.00	7 100%	0	0	0	0	0	0	0
Total	1738	0.34	1348 77.6%	265 15.3%	82 4.7%	19 1.1%	16 0.9%	5 0.3%	1 0.1%	2 0.1%

*OOA = Out of Area

Table IX.P-12. Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 10 mm, by Sex and Dose Category (continued)

B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Maximum Dimension ≥ 10 mm								
		Avg.	0	1	2	3	4	5	6	8
OOA	124	0.16	107 86.3%	14 11.3%	3 2.4%	0	0	0	0	0
< 10	185	0.20	156 84.3%	22 11.9%	6 3.2%	1 0.5%	0	0	0	0
10-49	314	0.18	267 85.0%	40 12.7%	5 1.6%	2 0.6%	0	0	0	0
50-99	310	0.19	270 87.1%	31 10.0%	4 1.3%	4 1.3%	0	0	0	1 0.3%
100-149	171	0.17	148 86.6%	19 11.1%	3 1.8%	0	1 0.6%	0	0	0
150-199	109	0.18	93 85.3%	14 12.8%	1 0.9%	0	1 0.9%	0	0	0
200-299	148	0.31	119 80.4%	19 12.8%	7 4.7%	1 0.7%	1 0.7%	0	1 0.7%	0
300-399	160	0.19	142 88.8%	13 8.1%	1 0.6%	2 1.3%	1 0.6%	1 0.7%	0	0
400-999	153	0.07	143 93.5%	9 5.9%	1 0.7%	0	0	0	0	0
1000+	17	0.35	14 82.4%	2 11.8%	0	0	1 5.9%	0	0	0
Total	1691	0.19	1459 86.3%	183 10.8%	31 1.8%	10 0.6%	5 0.3%	1 0.1%	1 0.1%	1 0.1%

*OOA = Out of Area

As shown in Table IX.P-13 participants had as many as six focal thyroid UDAs with average dimension ≥ 15 mm. Again, the majority (94% of women and 96% of men) had no such thyroid UDAs, and the overall average number of thyroid UDAs of this size was 0.07 for women and 0.05 for men.

Table IX.P-13. Number of Ultrasound-Detected Abnormalities of the Thyroid with Average Dimension ≥ 15 mm, by Sex and Dose Category

A. Female

Thyroid Radiation Dose (mGy)	Living Evaluable Female No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Average Dimension ≥ 15 mm					
		Avg.	0	1	2	3	6
OOA	124	0.03	120 96.8%	4 3.2%	0	0	0
< 10	182	0.06	172 94.5%	9 5.0%	1 0.6%	0	0
10-49	318	0.06	302 95.0%	13 4.1%	3 0.9%	0	0
50-99	311	0.06	295 94.9%	14 4.5%	1 0.3%	1 0.3%	0
100-149	220	0.08	207 94.1%	10 4.6%	2 0.9%	1 0.5%	0
150-199	125	0.12	111 88.8%	13 10.4%	1 0.8%	0	0
200-299	137	0.05	131 95.6%	5 3.7%	1 0.7%	0	0
300-399	143	0.08	132 92.3%	10 7.0%	1 0.7%	0	0
400-999	171	0.12	156 91.2%	11 6.4%	3 1.8%	1 0.6%	0
1000+	7	0.00	7 100%	0	0	0	0
Total	1738	0.07	1633 94.0%	89 5.1%	13 0.8%	3 0.2%	0

*OOA = Out of Area

Table IX.P-13. Number of Ultrasound-Detected Abnormalities of the Thyroid with Average Dimension ≥ 15 mm, by Sex and Dose Category (continued)

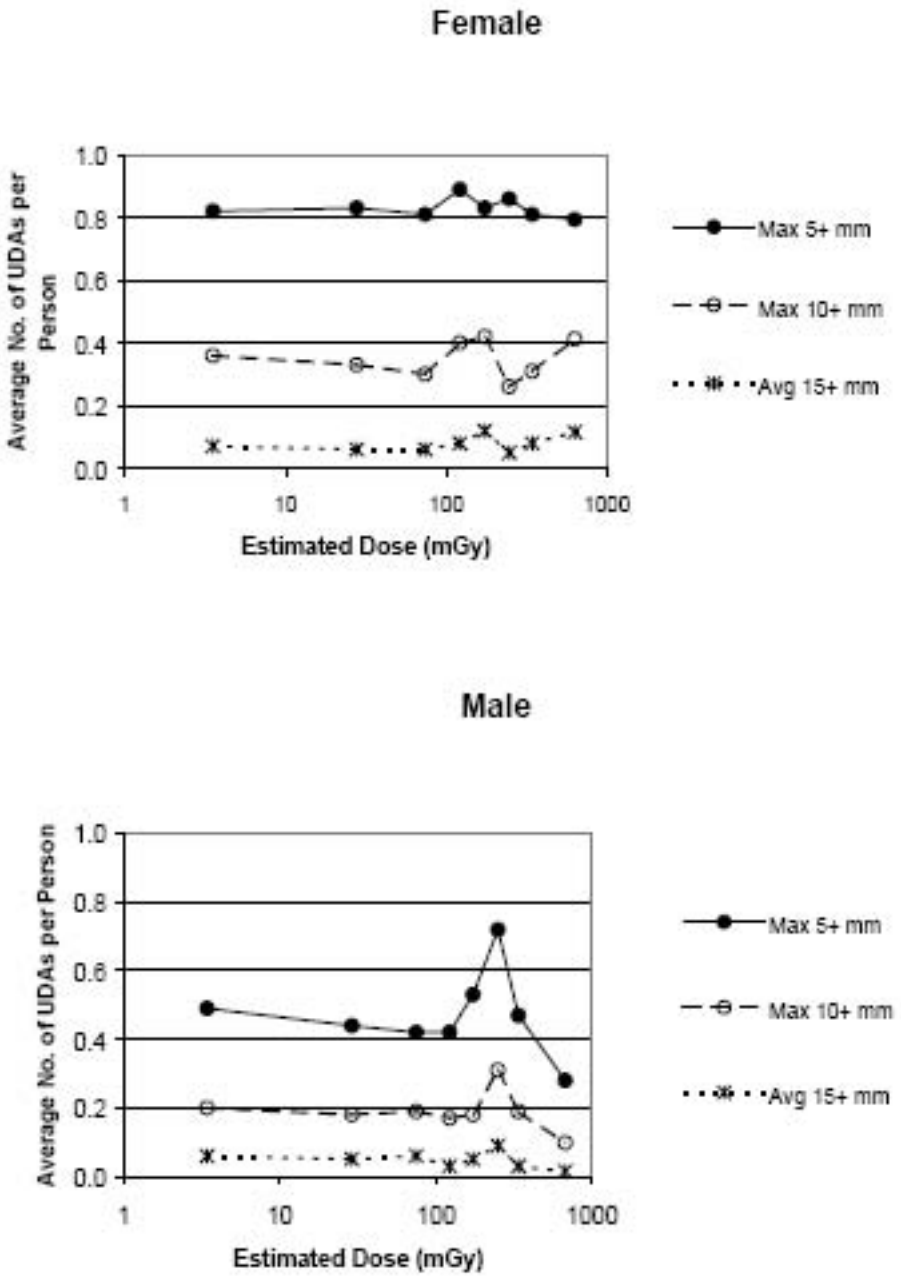
B. Male

Thyroid Radiation Dose (mGy)	Living Evaluable Male No.	Number of Ultrasound-Detected Abnormalities of the Thyroid with Average Dimension ≥ 15 mm					
		Avg.	0	1	2	3	6
OOA	124	0.02	122 98.4%	1 0.8%	1 0.8%	0	0
< 10	185	0.06	176 95.1%	7 3.8%	1 0.5%	1 0.5%	0
10-49	314	0.05	300 95.5%	13 4.1%	1 0.32%	0	0
50-99	310	0.06	298 96.1%	10 3.2%	1 0.3%	0	1 0.3%
100-149	171	0.03	167 97.7%	3 1.8%	1 0.6%	0	0
150-199	109	0.05	104 95.4%	5 4.6%	0	0	0
200-299	148	0.09	139 93.9%	5 3.4%	3 2.0%	1 0.7%	0
300-399	160	0.03	156 97.5%	4 2.5%	0	0	0
400-999	153	0.01	152 99.4%	1 0.7%	0	0	0
1000+	17	0.06	16 94.1%	1 5.9%	0	0	0
Total	1691	0.05	1630 96.4%	50 3.0%	8 0.5%	2 0.1%	1 0.1%

*OOA = Out of Area

Figure IX.P-3 below shows how the average numbers of thyroid UDAs per person, for each of the three size criteria, varied in relation to sex and estimated dose for living evaluable in-area participants. Due to the small number of participants in the 1000+ mGy dose category, it is combined with the 400-999 mGy category in Figure IX.P-3.

Figure IX.P-3. Average Number of Thyroid UDAs per Person, by Sex, Dose Category, and UDA Size



Results of fitting sex-stratified Poisson regression models for the relationship between estimated thyroid radiation dose and number of focal thyroid UDAs are summarized in Table IX.P-14 below. In this table, the estimated dose-response parameter represents the multiplicative change per Gy in the average number of thyroid UDAs per person. For none of these three size criteria did the average number of thyroid UDAs per person increase significantly with increasing estimated dose. For example, for focal thyroid UDAs with maximum dimension ≥ 5 mm, the average number of such thyroid UDAs per person decreased by an estimated factor of 1– 0.92 = 0.08 or 8% for each increase of 1 Gy in the estimated dose.

Consequently the average number of such thyroid UDAs per person did not increase significantly with estimated dose (p = 0.80). The Bonferroni-adjusted 95% confidence interval for the dose-response parameter ranged from 0.72 to 1.17, encompassing a range from a 28% decrease to a 17% increase per Gy.

Table IX.P-14. Poisson Regression Analyses of Numbers of Thyroid UDAs

Size Criterion For Focal Thyroid UDAs	Estimated Background Averages		Estimated Dose-response Parameter (per Gy)	Statistical Significance of Dose-response (one-tailed p-value)
	Female	Male		
Max ≥ 5 mm	0.84 (0.78, 0.91)	0.47 (0.42, 0.51)	0.92 (0.72, 1.17)	0.80
Max ≥ 10 mm	0.34 (0.30, 0.39)	0.19 (0.16, 0.22)	1.01 (0.70, 1.46)	0.48
Avg ≥ 15 mm	0.07 (0.06, 0.10)	0.05 (0.03, 0.06)	1.05 (0.50, 2.23)	0.43

For focal UDAs with average diameter ≥ 15 mm, the average number of such UDAs per person increased by an estimated factor of 1.05 – 1 = 0.05 or 5% for each increase of 1 Gy in the estimated dose (p = 0.43). The Bonferroni-adjusted 95% confidence interval for the dose-response parameter encompassed a range from a 50% decrease to a 123% increase per Gy.

P.3. Palpable Ultrasound-Detected Abnormalities of the Thyroid

Of the 3429 living evaluable participants whose thyroids were visible on the HTDS ultrasound, 224 (6.5%) had palpable ultrasound-detected abnormalities (Table IX.P-15). The ultrasound-detected thyroid abnormalities were based only on the HTDS evaluation.

Table IX.P-15. Proportion of Participants with HTDS Ultrasound Findings of Palpable Thyroid UDAs, by Sex

	Female		Male		Total	
Ultrasound Finding	No.	%	No.	%	No.	%
Thyroid Gland visible on ultrasound	1738	100.0	1691	100.0	3429	100.0
Palpable thyroid UDAs	154	8.9	70	4.1	224	6.5

P.3.a. Primary Analysis

The number and proportion of living evaluable participants with palpable thyroid UDAs is shown by sex, in-area status, and dose group in Table IX.P-16.

Table IX.P-16. Palpable Ultrasound-Detected Abnormalities by Sex and Estimated Dose

Thyroid Radiation Dose (mGy)	Female			Male		
	L.E. with Ultrasound	Palpable Thyroid UDA		L.E. with Ultrasound	Palpable Thyroid UDA	
	No.	No.	%	No.	No.	%
Out of Area	124	14	11.3	124	6	4.8
< 10	182	17	9.3	185	8	4.3
10-49	318	28	8.8	314	17	5.4
50-99	311	27	8.7	310	15	4.8
100-149	220	18	8.2	171	5	2.9
150-199	125	12	9.6	109	4	3.7
200-299	137	11	8.0	148	10	6.8
300-399	143	9	6.3	160	3	1.9
400-999	171	18	10.5	153	2	1.3
1000+	7	0	--	17	0	--
Total	1738	154	8.9	1691	70	4.1

L.E. = living evaluable participants

Of the 224 living evaluable participants with a palpable thyroid UDA, 20 were out-of-area participants. Parameter estimates for the linear dose-response model based on the 3181 in-area participants with ultrasound results are shown in Table IX.P-17. Based on maximum likelihood analysis of the sex-stratified linear probability model, the risk of having palpable thyroid UDA did not increase significantly with estimated dose ($p = 0.95$), with a negative estimated slope B of –0.018 per Gy (Table IX.P-17, row 1). The Bonferroni-adjusted lower 95% confidence limit was not estimated due to the magnitude of the negative slope estimate, however the upper confidence limit was 0.015 per Gy. Estimation by least squares using either the ungrouped or grouped data gave nearly identical results (Table IX.P-17, rows 2 and 3).

Table IX.P-17. Dose-Response Results for Diagnoses of Palpable Thyroid UDA

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition	Linear	Primary	None	MLE	.090 ± .008 (.070, .110)	.043 ± .006 (.029, .057)	–.018 ± .023 (NE, .015)	0.95
2.	Primary definition	Linear	Primary	None	LSU	.090 ± .007 (.074, .107)	.044 ± .007 (.027, .061)	–.020 ± .019 (–.066, .027)	0.85
3.	Primary definition	Linear	Primary	None	LSG	.091 ± .007 (.074, .109)	.046 ± .007 (.028, .063)	–.027 ± .022 (–.080, .026)	0.89
4.	Primary definition	LQ	Primary	None	MLE	.090 ± .008 (.072, .109)	.045 ± .008 (.026, .064)	Lin: –.022 ± .033 (–.103, .060) Quad: .002 ± .022 (–.053, .056)	Quad: 0.94

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.P-17. Dose-Response Results for Diagnoses of Palpable Thyroid UDA (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
5.	Primary definition	Logistic	Primary	None	MLE	.092 (.073, .115)	.043 (.031, .060)	–.38 ± .37 (–1.27, .51)	0.86
6.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.093 ± .008 (.073, .113)	.045 ± .006 (.031, .060)	–.030 ± .022 (< –.049, >.028)	0.90
7.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.091 ± .009 (.070, .112)	.051 ± .008 (.032, .069)	–.053 ± .040 (–.142, .049)	0.90
8.	Primary definition	Linear	Primary	Exclude OK and F/S geostrata	MLE	.088 ± .009 (.067, .109)	.041 ± .006 (.026, .056)	–.017 ± .023 (NE, .021)	0.92

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.P-17. Dose-Response Results for Diagnoses of Palpable Thyroid UDA (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
9.	Primary definition	Linear	Alt. #1	None	MLE	.090 ± .008 (.071, .109)	.044 ± .006 (.029, .059)	-.018 ± .020 (NE, .011)	0.96
10.	Primary definition	Linear	Alt. #2	None	MLE	.090 ± .008 (.070, .110)	.043 ± .006 (.029, .058)	-.019 ± .023 (NE, .003)	0.99
11.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.092 ± .008 (.073, .111)	.043 ± .006 (.030, .057)	-.018 ± .023 (NE, .014)	0.95
12.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.092 ± .008 (.073, .111)	.043 ± .006 (.030, .057)	-.018 ± .023 (NE, .012)	0.96

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

P.3.b. Alternative Dose-Response Functions

As shown in row 4 of Table IX.P-17, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was 0.002 with Bonferroni-adjusted 95% confidence interval ranging from –0.053 to 0.056. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.94$).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as –0.38 with Bonferroni-adjusted 95% confidence interval ranging from –1.27 to 0.51 (Table IX.P-17, row 5). Thus there was no evidence from the logistic regression model that prevalence of palpable thyroid UDAs increased with increasing dose ($p = 0.86$).

P.3.c. Effect of Excluding Participants in High Dose Categories

In the analyses excluding participants with estimated dose > 1000 mGy, the estimated slope B was negative (–0.030 per Gy, with Bonferroni-adjusted 95% CI ranging from less than –0.049 to greater than 0.028 per Gy), providing no evidence that the prevalence of palpable thyroid UDA increased with increasing dose ($p = 0.90$; Table IX.P-17, row 6). When participants with estimated dose > 400 mGy were excluded, the estimated slope B was again less than zero (–0.053 per Gy, with Bonferroni-adjusted 95% CI ranging from –0.142 to 0.049 per Gy), again providing no evidence that the prevalence of palpable thyroid UDA increased with increasing dose ($p = 0.90$; Table IX.P-17, row 7).

P.3.d. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

In the analyses excluding participants from the Okanogan and Ferry/Stevens Geostrata, the estimated slope B was negative, –0.017 per Gy, providing no evidence that the prevalence of palpable thyroid UDAs increased with increasing dose ($p = 0.92$; Table IX.P-17, row 8). The Bonferroni-adjusted lower 95% confidence limit was not estimated due to the magnitude of the negative slope estimate, however the upper confidence limit was 0.021 per Gy.

P.3.e. Analysis of Palpable Thyroid UDAs in Relation to Alternative Dose Estimates

For both alternative dose estimates the results were virtually the same as the primary analysis, providing no evidence that the prevalence of palpable thyroid UDAs increased with increasing dose (Table IX.P-17, rows 9 and 10).

P.3.f. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of the 249 out-of-area participants. For neither of the two scoping analyses was there any evidence that the prevalence of palpable thyroid UDAs increased with increasing dose ($p = 0.95$ and $p = 0.96$ for the first and second scoping analyses, respectively; Table IX.P-17, rows 11 and 12).

P.3.g. Analysis of Palpable Thyroid UDAs In Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of prevalence were performed as described in section VIII.C.2.a.2.

P.3.g.1. Analysis By Geostratum

As shown in Table IX.P-18, among the 3429 living evaluable in area or out-of-area participants with ultrasound results, the proportions with palpable UDAs ranged from 9/68 (13.2% in the Ferry/Stevens Counties geostratum) to 9/177 (5.1%, Richland) for women, and from 5/63 (7.9%, Okanogan County) to 13/501 (2.6%, Pasco/Kennewick) for men ($p = 0.051$ for heterogeneity among the nine geostrata). In particular the percentages with palpable UDAs were somewhat higher in the Okanogan and Ferry/Stevens geostrata (12.6% for women, 6.8% for men) than in the remaining geostrata (8.5% and 3.9%, respectively; $p = 0.0086$). Since it was likely that participants in the Okanogan and Ferry/Stevens geostrata tended to have lower thyroid doses from Hanford's ^{131}I than those in other geostrata, it does not appear that these differences can be attributed to an effect of Hanford's ^{131}I.).

Table IX.P-18. Palpable Ultrasound-Detected Abnormalities, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	177	9	5.1	172	5	2.9	349	14	4.0
Pasco/Kennewick	505	40	7.9	501	13	2.6	1006	53	5.3
Benton County	375	35	9.3	358	20	5.6	733	55	7.5
Franklin County	73	7	9.6	76	2	2.6	149	9	6.0
Adams County	165	14	8.5	156	10	6.4	321	24	7.5
Walla Walla (city)	131	14	10.7	131	5	3.8	262	19	7.3
Walla Walla County	169	17	10.1	164	6	3.7	333	23	6.9
Okanogan County	75	9	12.0	63	5	7.9	138	14	10.1
Ferry/Stevens Counties	68	9	13.2	70	4	5.7	138	13	9.4
Total	1738	154	8.9	1691	70	4.1	3429	224	6.5

P.3.g.2. Analysis by Dichotomous Exposure Variable

Ninety-five (7.6%) of the 1255 participants in these analyses had palpable thyroid UDAs, including 43/580 (7.4%) in the high exposure group and 52/675 (7.7%) in the low exposure group (Table IX.P-19). Thus the proportion of participants with palpable thyroid UDAs was not significantly elevated in the high exposure group ($p = 0.67$).

Table IX.P-19. Palpable Ultrasound-Detected Abnormalities, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	350	36	10.3	325	16	4.9	675	52	7.7
High	298	32	10.7	282	11	3.9	580	43	7.4
Total	648	68	10.5	607	27	4.4	1255	95	7.6

P.3.h. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results for palpable thyroid UDA might be influenced by confounding, and to search for factors that might modify a radiation dose-response. Table IX.P-20 displays results for models including sex, age at first exposure to Hanford ^{131}I (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type. Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. It is evident from Table IX.P-20 that the model was not significantly improved by adjusting for any of the other factors as a potential confounder: none produced a significantly better fit to the data. Since the estimated slope was virtually unaffected by such adjustments, it does not appear that omitting these factors introduces any important bias in the dose-response results.

There is no evidence of any statistically significant effect modification by any of the covariates in Table IX.P-20, with one possible exception. The dose-response was higher for the 1567 males (0.198) than for the 1614 females (0.067). The statistical significance of this difference must be interpreted with caution due to the large number of such comparisons that were performed. Moreover, neither males nor females had a significantly positive dose-response. Therefore, it does not appear that any of the covariates in Table IX.P-20 were significant effect modifiers for the outcome of palpable ultrasound-detected thyroid abnormalities.

Table IX.P-20. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid, and Interview Type: Palpable Thyroid UDAs

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1614 / 3181	-.382 ± .373 (–1.27, .510)	Not Applicable	.198 ± .226 (–4.28, .252)	.067 ± .228 (–.847, 1.07)	.019
Prenatal exposure?	1031 / 3181	-.382 ± .373 (–1.27, .510)	–.451 ± .381 (–1.43, .531)	–.441 ± .439 (–1.60, .719)	-.481 ± .763 (–2.49, 1.53)	.96
1st exposure before age 180 days?	1474 / 3181	-.382 ± .373 (–1.27, .510)	–.421 ± .383 (–1.41, .567)	–.167 ± .563 (–1.65, 1.32)	–.638 ± .552 (–2.09, .818)	.55
Age at exam > 50?	1993 / 3181	-.382 ± .373 (–1.27, .510)	–.413 ± .381 (–1.39, .568)	–.578 ± .738 (–2.53, 1.37)	–.348 ± .446 (–1.53, .829)	.79
NTS I-131 dose > 5.3 mGy?	1563 / 3179	-.382 ± .373 (–1.27, .511)	–.385 ± .382 (–1.37, .600)	–.243 ± .479 (–1.51, 1.02)	–.615 ± .648 (–2.33, 1.10)	.64
History of any cancer other than thyroid?	248 / 3176	–.381 ± .373 (–1.27, .510)	–.381 ± .375 (–1.35, .585)	–.434 ± .406 (–1.51, .638)	–.072 ± .886 (–2.41, 2.26)	.72
Expanded In-Person Interview?	1205 / 3181	-.382 ± .373 (–1.27, .510)	–.318 ± .376 (–1.29, .651)	.068 ± .515 (–1.29, 1.43)	–.744 ± .604 (–2.34, .849)	.30

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.P-21 and IX.P-22 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. There is no evidence of any confounding or statistically significant effect modification.

Table IX.P-21. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Palpable Thyroid UDAs

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding. Estimate	Including Effect Modification		
				Group 0	Group 1	P
CAT scan of the upper body?	775 / 3139	−.424 ± .381 (−1.34, .488)	−.407 ± .376 (−1.38, .562)	−.240 ± .383 (−1.25, .772)	−1.59 ± 1.15 (−4.62, 1.43)	.24
Diagnostic x-rays of the head?	1188 / 3145	−.335 ± .370 (−1.22, .550)	−.337 ± .369 (−1.29, .614)	−.285 ± .442 (−1.45, .882)	−.449 ± .665 (−2.20, 1.31)	.84
Diagnostic x-rays of the neck?	960 / 3157	−.362 ± .371 (−1.25, .527)	−.362 ± .373 (−1.32, .599)	−.020 ± .447 (−1.20, 1.16)	−1.05 ± .738 (−3.00, .891)	.21
Diagnostic x-rays of chest or upper body, including mammograms?	2811 / 3163	−.372 ± .372 (−1.26, .519)	−.352 ± .372 (−1.31, .607)	−1.57 ± 1.66 (−5.94, 2.81)	−.272 ± .377 (−1.27, .723)	.42
Diagnostic x-rays of the stomach or mid-back?	691 / 3110	−.411 ± .385 (−1.33, .510)	−.413 ± .385 (−1.40, .578)	−.159 ± .393 (−1.20, .879)	−2.04 ± 1.20 (−5.21, 1.14)	.11
Barium enema?	821 / 3149	−.378 ± .373 (−1.27, .514)	−.375 ± .373 (−1.34, .585)	−.368 ± .427 (−1.50, .759)	−.398 ± .763 (−2.41, 1.61)	.97
Upper GI?	1140 / 3167	−.368 ± .372 (−1.26, .522)	−.367 ± .372 (−1.32, .591)	−.001 ± .411 (−1.09, 1.08)	−1.20 ± .730 (−3.13, .721)	.14
Intravenous pyelogram?	396 / 3147	−.391 ± .376 (−1.29, .508)	−.378 ± .376 (−1.35, .591)	−.266 ± .387 (−1.29, .754)	−1.31 ± 1.23 (−4.55, 1.92)	.40
Fluoroscopy of the upper body?	246 / 3151	−.349 ± .373 (−1.24, .544)	−.352 ± .373 (−1.31, .610)	−.242 ± .374 (−1.23, .745)	−2.27 ± 1.91 (−7.31, 2.76)	.24
Other nuclear scan?	216 / 3152	−.386 ± .375 (−1.28, .511)	−.395 ± .375 (−1.36, .571)	−.307 ± .378 (−1.31, .691)	−1.92 ± 1.85 (−6.80, 2.95)	.35
Dental x-rays that did not usually include a lead shield over the neck area?	1644 / 3181	.382 ± .373 (−1.27, .510)	−.385 ± .374 (−1.35, .578)	−.173 ± .483 (−1.45, 1.10)	−.658 ± .589 (−2.21, .895)	.52

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-22. Confounding and Effect Modification by Occupational History: Palpable Thyroid UDAs

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification		
				Group 0	Group 1	P
Any metal industry?	238 / 3181	.382 ± .373 (–1.27, .510)	–.373 ± .372 (–1.33, .586)	–.379 ± .378 (–1.38, .619)	–.166 ± 2.14 (–5.81, 5.48)	.92
Any nuclear facility?	370 / 3181	.382 ± .373 (–1.27, .510)	–.378 ± .375 (–1.34, .589)	–.212 ± .386 (–1.23, .807)	–1.67 ± 1.27 (–5.01, 1.67)	.24
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3181	.382 ± .373 (–1.27, .510)	–.402 ± .375 (–1.37, .563)	–.186 ± .379 (–1.18, .813)	–3.30 ± 1.89 (–8.30, 1.69)	.06
Any of the above industries or occupations?	891 / 3181	.382 ± .373 (–1.27, .510)	–.346 ± .372 (–1.30, .612)	–.111 ± .398 (–1.16, .938)	–1.34 ± .957 (–3.86, 1.18)	.21

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-23 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.P-23. Confounding and Effect Modification by Smoking: Palpable Thyroid UDAs

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy)				
		Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification		
				Group 0	Group 1	P
Cigarettes (unfiltered or filtered)?	1850 / 3173	–.371 ± .372 (–1.26, .520)	–.373 ± .372 (–1.33, .585)	–.416 ± .608 (–2.02, 1.19)	–.346 ± .468 (–1.58, .888)	.93
Any of cigarettes, cigar or pipe?	1896 / 3173	–.371 ± .372 (–1.26, .520)	–.372 ± .372 (–1.33, .585)	–.291 ± .607 (–1.89, 1.31)	–.421 ± .474 (–1.67, .829)	.87

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

P.3.i. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for the outcome of palpable thyroid UDA are shown in Figure IX.P-4 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific

background rates. While the point estimate of the slope is greater than 0 for 1 of the 100 realizations, the confidence interval includes 0 for all of the realizations. Also shown in Figure IX.P-4 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for none of the 100 realizations of the estimated doses was there a statistically significant dose-response, and for all but one realization the estimated slope was less than 0.

Figure IX.P-4. Plot of Estimated Slope and 95% CI by Dose Realization: Palpable Thyroid UDAs

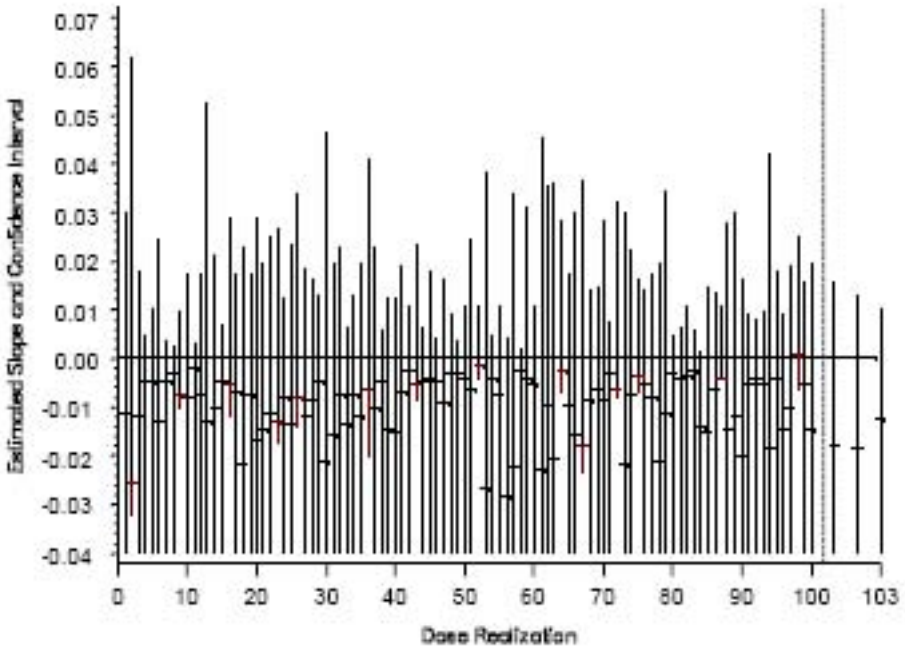
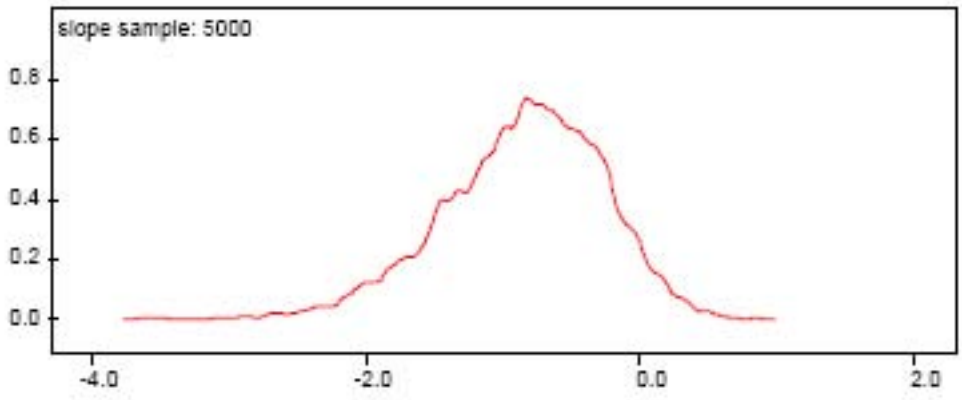


Figure IX.P-5 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –3.0 and 0.3. The estimate was less than or equal to 0 for 4735 of the 5000 replications, implying an empirical one-tailed p-value of 0.95. The median estimate was –0.80, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –2.42 and 0.33. These may be compared to the p-value of 0.21 and the estimate of –0.38 with confidence interval (–1.27, 0.51) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the prevalence of palpable thyroid UDA increased with increasing dose.

Figure IX.P-5. Distribution of Simulation Estimates of Logistic Regression Coefficient: Palpable Thyroid UDAs



P.4. Nonpalpable Focal Ultrasound-Detected Abnormalities of the Thyroid

Among the 3429 whose thyroids were visible, 1309 (38.2%) had nonpalpable focal thyroid UDAs. The ultrasound-detected thyroid abnormalities were based only on the HTDS evaluation (Table IX.P-24).

Table IX.P-24. Proportion of Participants with HTDS Ultrasound Findings of Nonpalpable Focal Thyroid UDAs, by Sex

	Female		Male		Total	
Ultrasound Finding	No.	%	No.	%	No.	%
Thyroid gland visible on ultrasound	1738	100.0	1691	100.0	3429	100.0
Nonpalpable focal thyroid UDAs	784	45.1	525	31.0	1309	38.2

P.4.a. Primary Analysis

The proportion with nonpalpable focal thyroid UDAs is shown by sex, in-area status, and dose group in Table IX.P-25.

Table IX.P-25. Nonpalpable Ultrasound-Detected Abnormalities by Sex, and Estimated Dose: Participants with Ultrasound Only

	Female			Male		
Thyroid Radiation Dose	L.E. with Ultrasound	Nonpalpable Focal Thyroid UDA		L.E. with Ultrasound	Nonpalpable Focal Thyroid UDA	
(mGy)	No.	No.	%	No.	No.	%
Out of Area	124	49	39.5	124	43	34.7
< 10	182	81	44.5	185	57	30.8
10-49	318	138	43.4	314	91	29.0
50-99	311	140	45.0	310	84	27.1
100-149	220	109	49.5	171	52	30.4
150-199	125	53	42.4	109	38	34.9
200-299	137	70	51.1	148	56	37.8
300-399	143	65	45.5	160	58	36.3
400-999	171	78	45.6	153	36	23.5
1000+	7	1	14.3	17	10	58.8
Total	1738	784	45.1	1691	525	31.0

L.E. = living evaluable participants

Of the 1309 living evaluable participants with a nonpalpable focal thyroid UDA, 92 were out-of-area participants. Parameter estimates for the linear dose-response model based on the 3181 in-area participants are show in Table IX.P-26 below. The estimated slope B was not significantly greater than zero (0.027 per Gy, with Bonferroni-adjusted 95% confidence interval ranging from -0.061 to 0.115), providing no evidence that the prevalence of nonpalpable thyroid UDAs increased with increasing dose ($p = 0.23$; Table IX.P-26, row 1). Estimation by least squares using either the ungrouped or grouped data gave similar results (Table IX.P-26, rows 2 and 3).

Table IX.P-26. Dose-Response Results for Diagnoses of Nonpalpable Focal Thyroid UDAs

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition	Linear	Primary	None	MLE	.451 ± .014 (.417, .484)	.303 ± .013 (.270, .335)	.027 ± .037 (-.061, .115)	0.23
2.	Primary definition	Linear	Primary	None	LSU	.451 ± .014 (.419, .484)	.303 ± .014 (.270, .337)	.024 ± .038 (–.067, .115)	0.27
3.	Primary definition	Linear	Primary	None	LSG	.453 ± .014 (.419, .487)	.305 ± .014 (.271, .340)	.014 ± .044 (–.091, .119)	0.38
4.	Primary definition	LQ	Primary	None	LSU	.442 ± .015 (.405, .479)	.294 ± .015 (.256, .331)	Lin: .111 ± .064 (–.050, .272) Quad: –.072 ± .043 (–.178, .035)	Quad: 0.093

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.P-26. Dose-Response Results for Diagnoses of Nonpalpable Focal Thyroid UDAs (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
5.	Primary definition	Logistic	Primary	None	MLE	.451 (.417, .485)	.304 (.273, .336)	.10 ± .16 (-.29, .49)	0.27
6.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.452 ± .015 (.417, .487)	.300 ± .014 (.266, .333)	.029 ± .048 (<-.085, .145)	0.27
7.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.431 ± .016 (.392, .470)	.285 ± .016 (.247, .323)	.228 ± .085 (.026, .431)	0.003
8.	Primary definition	Linear	Primary	Exclude OK and F/S geostrata	MLE	.449 ± .015 (.413, .484)	.295 ± .014 (.261, .329)	.037 ± .038 (-.053, .125)	0.16

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

Table continued on next page

Table IX.P-26. Dose-Response Results for Diagnoses of Nonpalpable Focal Thyroid UDAs (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
9.	Primary definition	Linear	Alt. #1	None	MLE	.454 ± .014 (.420, .488)	.306 ± .014 (.273, .339)	.007 ± .037 (-.079, .095)	0.43
10.	Primary definition	Linear	Alt. #2	None	MLE	.446 ± .014 (.412, .480)	.298 ± .014 (.265, .330)	.052 ± .038 (-.038, .142)	0.085
11.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.446 ± .013 (.414, .478)	.305 ± .013 (.275, .336)	.031 ± .037 (-.056, >.117)	0.20
12.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.447 ± .013 (.415, .479)	.306 ± .013 (.276, .337)	.025 ± .037 (<-.062, .111)	0.25

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

P.4.b. Alternative Dose-Response Functions

As shown in row 4 of Table IX.P-26, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was –0.072 with Bonferroni-adjusted 95% confidence interval ranging from –0.178 to 0.035. Thus the addition of a quadratic term did not significantly improve the fit of the model ($p = 0.093$).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.10, with Bonferroni-adjusted 95% confidence interval ranging from –0.29 to 0.49 (Table IX.P-26, row 5). Thus there was no evidence from the logistic regression model that prevalence of nonpalpable focal thyroid UDA increased significantly with increasing dose ($p = 0.27$).

P.4.c. Effect of Excluding Participants in High Dose Categories

As shown in row 7 of Table IX.P-26 above, the estimated slope of the dose-response for nonpalpable focal thyroid UDAs was larger if participants with highest estimated doses were excluded. In particular, when participants with estimated dose > 400 mGy were excluded, the estimated slope B increased from 0.027 to 0.228 per Gy ($p = 0.003$). Excluding the small number of participants with estimated dose > 1000 mGy had very little effect on the estimated dose-response (Table IX.P-26, row 6).

P.4.d. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

As shown in row 8 of Table IX.P-26, excluding Okanogan and Ferry/Stevens slightly reduced the estimated background rates for both men and women. The reductions were small, because the Okanogan and Ferry/Stevens geostrata account for only 255 (8.0%) of the 3181 in-area living evaluable participants with ultrasound results. As a result of these reductions in the background rates and the fact that Okanogan and Ferry/Stevens geostrata tend to have low doses, the estimated slope changed slightly, from 0.027 to 0.037 per Gy, but remained statistically nonsignificant ($p = 0.16$).

P.4.e. Analysis of Nonpalpable Focal Thyroid UDAs in Relation to Alternative Dose Estimates

Using the first alternative set of dose estimates, the estimated slope changed slightly, to 0.007 per Gy, with Bonferroni-adjusted 95% confidence limits –0.079 and 0.095 per Gy, which does not represent a statistically significant dose-response for nonpalpable focal thyroid UDAs ($p = 0.43$; Table IX.P-26, row 9). Similar results were obtained using the second alternative dose estimates, with estimated slope 0.052 per Gy and 95% CI ranging from –0.038 to 0.142 ($p = 0.085$; Table IX.P-26, row 10).

P.4.f. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of the 249 out-of-area participants. The results of both scoping analyses were virtually the same as the primary analysis and provided no evidence that the prevalence of nonpalpable focal thyroid UDA increased with increasing dose (Table IX.P-7). For neither set of scoping analyses was there evidence that the proportion with nonpalpable focal thyroid UDAs increased with increasing dose ($p = 0.20$ for the first scoping analysis, and $p = 0.25$ for the second scoping analysis; Table IX.P-26, rows 11 and 12).

P.4.g. Analysis of Nonpalpable Focal Thyroid UDAs in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of prevalence were performed as described in section VIII.C.2.a.2.

P.4.g.1. Analysis by Geostratum

The proportions of women with nonpalpable focal thyroid UDAs ranged from 69/131 (52.7%) in the Walla Walla city geostratum to 75/177 (42.4%) in the Richland geostratum (Table IX.P-27). For men they ranged from 32/76 (42.1%) in the Franklin geostratum to 31/164 (18.9%) in the Walla Walla County geostratum. The heterogeneity among the nine geostrata was not statistically significant (p = 0.083). The proportions were somewhat higher in the Okanogan and Ferry/Stevens geostrata (46.2% and 38.3% for women and men, respectively) compared to the other geostrata (45.0% and 30.4%, respectively), also a nonsignificant difference for the heterogeneity between combined geostrata (p = 0.082).

Table IX.P-27. Nonpalpable Focal Ultrasound-Detected Abnormalities, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	177	75	42.4	172	48	27.9	349	123	35.2
Pasco/Kennewick	505	227	45.0	501	156	31.1	1006	383	38.1
Benton County	375	164	43.7	358	114	31.8	733	278	37.9
Franklin County	73	35	47.9	76	32	42.1	149	67	45.0
Adams County	165	74	44.8	156	57	36.5	321	131	40.8
Walla Walla (city)	131	69	52.7	131	36	27.5	262	105	40.1
Walla Walla County	169	74	43.8	164	31	18.9	333	105	31.5
Okanogan County	75	33	44.0	63	26	41.3	138	59	42.8
Ferry/Stevens Counties	68	33	48.5	70	25	35.7	138	58	42.0
Total	1738	784	45.1	1691	525	31.0	3429	1309	38.2

P.4.g.2. Analysis by Dichotomous Exposure Variable

A total of 494 (39.4%) of the 1255 participants in these analyses had nonpalpable focal thyroid UDAs, including 240/580 (41.4%) in the high exposure group and 254/675 (37.6%) in the low exposure group (Table IX.P-28). Based on the logistic regression analysis with adjustment for the effect of sex and age at HTDS examination, the proportion of participants with nonpalpable focal thyroid UDA was not significantly elevated in the high exposure group (p = 0.081).

Table IX.P-28. Nonpalpable Focal Ultrasound-Detected Abnormalities, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	350	154	44.0	325	100	30.8	675	254	37.6
High	298	149	50.0	282	91	32.3	580	240	41.4
Total	648	303	46.8	607	191	31.5	1255	494	39.4

P.4.h. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. Table IX.P-29 displays results for models including sex, age at first exposure to Hanford I-131 (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type. Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model.

It is evident from Table IX.P-29 that the estimated slope was virtually unaffected by adjustments for possible confounding. Therefore, it does not appear that omitting these factors introduces any important bias in the dose-response results. In addition, the regression coefficients did not differ significantly between the groups defined by any of the covariates, suggesting that none of them were significant modifiers of a radiation dose-response for nonpalpaple UDAs.

Table IX.P-29. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid, and Interview Type: Nonpalpable Focal Ultrasound-Detected Abnormalities

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted Estimate	Incl. Confounding. Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1614 / 3181	.102 ± .164 (–.290, .494)	Not Applicable	.198 ± .226 (–.208, .949)	.067 ± .228 (–.724, .422)	.11
Prenatal exposure?	1031 / 3181	.102 ± .164 (–.290, .494)	.045 ± .165 (–.381, .471)	.137 ± .189 (–.360, .634)	–.261 ± .349 (–1.18, .659)	.31
1st exposure before age 180 days?	1474 / 3181	.102 ± .164 (–.290, .494)	.092 ± .165 (–.333, .517)	.516 ± .280 (–.224, 1.26)	–.135 ± .210 (–.690, .419)	.062
Age at exam > 50?	1993 / 3181	.102 ± .164 (–.290, .494)	.111 ± .166 (–.317, .538)	–.183 ± .308 (–.996, .630)	.236 ± .198 (–.286, .758)	.25
NTS I-131 dose > 5.3 mGy?	1563 / 3179	.096 ± .164 (–.296, .488)	.063 ± .167 (–.368, .495)	.116 ± .221 (–.467, .698)	–.007 ± .258 (–.689, .675)	.72
History of any cancer other than thyroid?	248 / 3176	.103 ± .164 (–.289, .495)	.107 ± .164 (–.315, .529)	.193 ± .177 (–.275, .661)	–.413 ± .474 (–1.66, .837)	.21
Expanded In-Person Interview?	1205 / 3181	.102 ± .164 (–.290, .494)	.106 ± .167 (–.324, .535)	.401 ± .266 (–.300, 1.10)	–.085 ± .217 (–.658, .488)	.16

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.P-30 and IX.P-31 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. There was no evidence of confounding, or of clearly significant effect modification, by any of these variables.

Table IX.P-30. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Nonpalpable Focal Ultrasound-Detected Abnormalities

Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted Estimate	Incl. Confounding. Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
CAT scan of the upper body?	775 / 3139	.102 ± .164 (–.292, .495)	.102 ± .164 (–.321, .525	–.030 ± .182 (–.509, .450)	.746± .397 (–.302, 1.79)	.08
Diagnostic x-rays of the head?	1188 / 3145	.103 ± .165 (–.292, .498)	.099 ± .165 (–.327, .524)	.242 ± .204 (–.296, .779)	–.181 ± .290 (–.947, .584)	.23
Diagnostic x-rays of the neck?	960 / 3157	.094 ± .165 (–.300, .487)	.100 ± .165 (–.325, .525)	.012 ± .217 (–.560, .585)	.223 ± .257 (–.454, .900)	.53
Diagnostic x-rays of chest or upper body, including mammograms?	2811 / 3163	.098 ± .164 (–.294, .491)	.103 ± .164 (–.320, .526)	.270 ± .590 (–1.29, 1.83)	.089 ± .171 (–.361, .540)	.77
Diagnostic x-rays of the stomach or mid-back?	691 / 3110	.128 ± .166 (–.268, .524)	.131 ± .166 (–.296, .557)	.068 ± .186 (–.423, .559)	.379 ± .370 (–.596, 1.35)	.45
Barium enema?	821 / 3149	.104 ± .164 (–.289, .497)	.105 ± .164 (–.318, .528)	.104 ± .191 (–.400, .608)	.107 ± .321 (–.740, .954)	.99
Upper GI?	1140 / 3167	.100 ± .164 (–.292, .493)	.099 ± .164 (–.323, .521)	.009 ± .208 (–.539, .557)	.252 ± .270 (–.459, .964)	.47
Intravenous pyelogram?	396 / 3147	.102 ± .165 (–.292, .496)	.104 ± .165 (–.320, .528)	.108 ± .175 (–.354, .569)	.072 ± .487 (–1.21, 1.36)	.94
Fluoroscopy of the upper body?	246 / 3151	.118 ± .164 (–.275, .511)	.119 ± .164 (–.305, .542)	.090 ± .171 (–.361, .542)	.477 ± .603 (–1.11, 2.07)	.54
Other nuclear scan?	216 / 3152	.092 ± .164 (–.301, .486)	.093 ± .164 (–.331, .516)	.155 ± .169 (–.291, .602)	–.903 ±.709 (–2.77, .966)	.13
Dental x-rays that did not usually include a lead shield over the neck area?	1644 / 3181	.102 ± .164 (–.290, .494)	.103 ± .164 (–.319, .524)	.212 ± .233 (–.403, .827)	–.003 ± .230 (–.610, .605)	.51

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-31. Confounding and Effect Modification by Occupational History: Nonpalpable Focal Ultrasound-Detected Abnormalities

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Group 1	P
Any metal industry?	238 / 3181	.102 ± .164 (–.290, .494)	.098 ± .164 (–.323, .520)	.071 ± .169 (–.374, .516)	.565 ± .685 (–1.24, 2.37)	.49
Any nuclear facility?	370 / 3181	.102 ± .164 (–.290, .494)	.099 ± .165 (–.326, .525)	–.010 ± .183 (–.493, .474)	.588 ± .385 (–.427, 1.60)	.16
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3181	.102 ± .164 (–.290, .494)	.101 ± .164 (–.321, .522)	.176 ± .180 (–.300, .652)	–.260 ± .413 (–1.35, .829)	.32
Any of the above industries or occupations?	891 / 3181	.102 ± .164 (–.290, .494)	.110 ± .164 (–.312, .533)	.047 ± .202 (–.487, .580)	.233 ± .280 (–.506, .972)	.59

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

Table IX.P-32 displays the results of analyses of possible confounding or effect modification by smoking variables. There was some evidence that the dose-response coefficient differed between participants with versus without histories of smoking cigarettes ($p = 0.033$) or any of cigarettes, cigars or pipes ($p = 0.019$). The estimated dose-response coefficients were greater than zero among nonsmokers, but negative for smokers. However, the Bonferroni-adjusted 95% confidence intervals for the smokers' and nonsmokers' estimated coefficients overlapped, including the value of zero in the overlap. In view of the significance levels of these two tests for effect modification and the large number of comparisons performed in these analyses, these results do not provide compelling evidence of a statistically significant dose-response within the nonsmoking cohort.

Table IX.P-32. Confounding and Effect Modification by Smoking: Nonpalpable Focal Ultrasound-Detected Abnormalities

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Estimate	Adjusted for Estimate	Including Effect Modification Group 0	Group 1	P
Cigarettes (unfiltered or filtered)?	1850 / 3173	.108 ± .164 (–.284, .500)	.107 ± .164 (–.315, .529)	.589 ± .279 (–.148, 1.33)	–.150 ± .208 (–.699, .398)	.033
Any of cigarettes, cigar or pipe?	1896 / 3173	.108 ± .164 (–.284, .500)	.107 ± .164 (–.315, .529)	.648 ± .284 (–.100, 1.40)	–.172 ± .207 (–.718, .375)	.019

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values reflect the significance of the improved fit for models including confounding or effect modification, relative to the unadjusted model.

P.4.i. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for the outcome of nonpalpable focal thyroid UDA are shown in Figure IX.P-6 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 85 of the 100 realizations, the confidence interval includes 0 for all but 1 of the realizations. Also shown in Figure IX.P-6 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for only one of the 100 realizations of the estimated doses was there a statistically significant dose-response, although for most of the realizations the estimated slope was greater than 0.

Figure IX.P-6. Plot of Estimated Slope and 95% CI by Dose Realization: Nonpalpable Focal Ultrasound-Detected Abnormalities

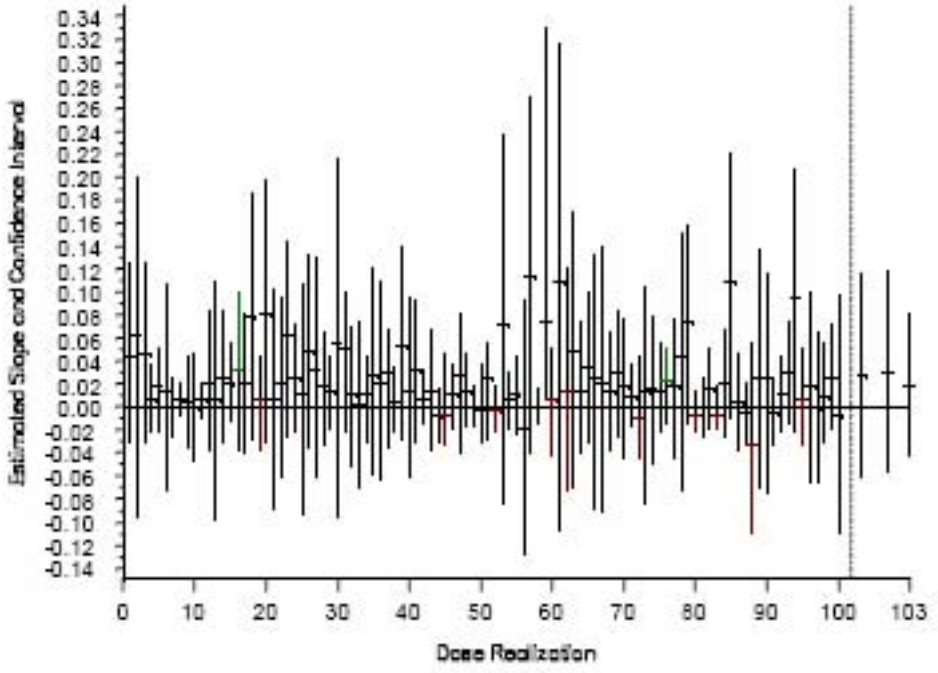
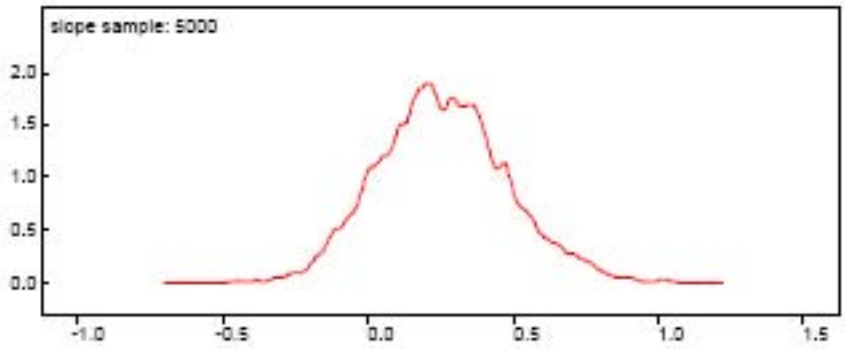


Figure IX.P-7 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –0.5 and 1.0. The estimate was less than or equal to 0 for 604 of the 5000 replications, implying an empirical one-tailed p-value of 0.12. The median estimate was –0.25, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –0.27 and 0.84. These may be compared to the p-value of 0.27 and the estimate of 0.10 with confidence interval (–0.29, 0.49) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the prevalence of nonpalpable focal thyroid UDA increased significantly with increasing dose.

Figure IX.P-7. Distribution of Simulation Estimates of Logistic Regression Coefficient: Nonpalpable Focal Ultrasound-Detected Abnormalities



P.5. Diffuse Ultrasound-Detected Abnormalities of the Thyroid

Of the 3429 living evaluable participants whose thyroids were visible, 458 (13.4%) had diffuse ultrasound-detected thyroid abnormalities (Table IX.P-33).

Table IX.P-33. Proportion of Participants with HTDS Ultrasound Findings of Diffuse Thyroid UDAs, by Sex

	Female		Male		Total	
Ultrasound Finding	No.	%	No.	%	No.	%
Thyroid gland visible on ultrasound	1738	100.0	1691	100.0	3429	100.0
Diffuse thyroid UDAs	306	17.6	152	9.0	458	13.4

P.5.a. Primary Analysis

Of the 458 living evaluable participants with a diagnosis of diffuse thyroid UDAs, 30 were out-of-area participants. The proportions with diffuse thyroid UDAs are shown by sex, in-area status and dose group in Table IX.P-34.

Table IX.P-34. Diffuse Ultrasound-Detected Abnormalities by Sex, and Estimated Dose: Participants with Ultrasound Only

Thyroid Radiation Dose (mGy)	Female			Male		
	L.E. with Ultrasound	Diffuse Ultrasound-Detected Abnormality		L.E. with Ultrasound	Diffuse Ultrasound Detected Abnormality	
	No.	No.	%	No.	No.	%
Out of Area	124	18	14.5	124	12	9.7
< 10	182	29	15.9	185	19	10.3
10-49	318	53	16.7	314	21	6.7
50-99	311	47	15.1	310	22	7.1
100-149	220	52	23.6	171	17	9.9
150-199	125	25	20.0	109	9	8.3
200-299	137	24	17.5	148	21	14.2
300-399	143	30	21.0	160	18	11.3
400-999	171	27	15.8	153	11	7.2
1000+	7	1	14.3	17	2	11.8
Total	1738	306	17.6	1691	152	9.0

L.E. = living evaluable participants

Parameter estimates for the linear dose-response model based on the 3181 in-area participants with a visible thyroid are shown in Table IX.P-35 below. The estimated slope B was not significantly greater than zero (0.029 per Gy with Bonferroni-adjusted 95% confidence interval ranging from 0.029 to 0.100) providing no evidence that the proportion with diffuse thyroid UDAs increased with increasing dose ($p = 0.14$; Table IX.P-35, row 1). Estimating by least squares using either the ungrouped or grouped data gave similar results (Table IX.P-35, rows 2 and 3).

Table IX.P-35. Dose-Response Results for Diagnoses of Diffuse Ultrasound Abnormalities

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
1.	Primary definition	Linear	Primary	None	MLE	.174 ± .011 (.148, .199)	.084 ± .009 (.064, .105)	.029 ± .028 (-.029, .100)	0.14
2.	Primary definition	Linear	Primary	None	LSU	.174 ± .010 (.151, .197)	.085 ± .010 (.061, .108)	.026 ± .027 (-.039, .090)	0.17
3.	Primary definition	Linear	Primary	None	LSG	.176 ± .010 (.153, .200)	.087 ± .010 (.063, .111)	.013 ± .031 (-.061, .086)	0.34
4.	Primary definition	LQ	Primary	None	LSU	.174 ± .010 (.148, .200)	.085 ± .011 (.058, .111)	Lin: .027 ± .045 (–.086, .140) Quad: –.001 ± .030 (–.076, .074)	Quad: 0.97

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.P-35. Dose-Response Results for Diagnoses of Diffuse Ultrasound Abnormalities (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
5.	Primary definition	Logistic	Primary	None	MLE	.173 (.149, .201)	.086 (.070, .107)	.21 ± .22 (-.32, .74)	0.17
6.	Primary definition	Linear	Primary	Exclude dose > 1000 mGy	MLE	.173 ± .011 (.147, .199)	.084 ± .009 (.062, .105)	.033 ± .034 (<-.043, >.118)	0.16
7.	Primary definition	Linear	Primary	Exclude dose > 400 mGy	MLE	.164 ± .012 (.136, .193)	.074 ± .010 (.051, .097)	.146 ± .059 (.010, .291)	0.005
8.	Primary definition	Logistic	Primary	Exclude OK and F/S geostrata	MLE	.172 ± .011 (.146, .199)	.075 ± .009 (.054, .097)	.042 ± .029 (-.021, .115)	0.065

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

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Table IX.P-35. Dose-Response Results for Diagnoses of Diffuse Ultrasound Abnormalities (continued)

Row	Outcome	Dose-Response Model	Dose Estimates	Exclusions / Additional Inclusions	Method of Analysis	Estimated Background Rates		Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
						Female	Male		
9.	Primary definition	Linear	Alt. #1	None	MLE	.176 ± .011 (.151, .202)	.087 ± .009 (.066, .108)	.010 ± .026 (<-.041, .078)	0.34
10.	Primary definition	Linear	Alt. #2	None	MLE	.176 ± .011 (.151, .201)	.087 ± .009 (.066, .108)	.013 ± .026 (-.037, .080)	0.30
11.	Primary definition	Linear	Primary	Include OOA (scoping analysis #1)	MLE	.171 ± .010 (.147, .195)	.085 ± .008 (.065, .104)	.031 ± .027 (-.027, >.101)	0.12
12.	Primary definition	Linear	Primary	Include OOA (scoping analysis #2)	MLE	.172 ± .010 (.148, .196)	.085 ± .008 (.066, .105)	.028 ± .027 (<-.029, >.097)	0.14

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). Standard errors are not given for estimated background rates from logistic regression model.

Abbreviations: MLE = maximum likelihood estimation, LSU = least squares estimation with ungrouped doses, LSG = least squares estimation with grouped doses, LQ = linear-quadratic, Ok = Okanogan, F/S = Ferry/Stevens, OOA = out of area

P.5.b. Alternative Dose-Response Functions

As shown in row 4 of Table IX.P-35, the estimated regression coefficient for the dose-squared term in the linear-quadratic dose-response model [5] was –0.001 with Bonferroni-adjusted 95% confidence interval ranging from –0.076 to 0.074. Thus the addition of a quadratic term did not significantly improve the fit of the model (p = 0.97).

The regression parameter for the effect of dose in the sex-stratified logistic regression model [2] was estimated as 0.21, with Bonferroni-adjusted 95% confidence interval ranging from –0.32 to 0.74 (Table IX.P-35, row 5). Thus there was no evidence from the logistic regression model that prevalence of diffuse thyroid UDA increased significantly with increasing dose (p = 0.17).

P.5.c. Effect of Excluding Participants in High Dose Categories

As shown in row 7 of Table IX.P-35 above, the estimated slope of the dose-response for nonpalpable focal thyroid UDAs was larger if participants with highest estimated doses were excluded. In particular, when participants with estimated dose > 400 mGy were excluded, the estimated slope B increased from 0.029 to 0.146 per Gy (p = 0.005). Excluding the small number of participants with estimated dose > 1000 mGy had very little effect on the estimated dose-response (Table IX.P-35, row 6).

P.5.d. Effect of Excluding Okanogan and Ferry/Stevens Geostrata

The effect of excluding the Okanogan and Ferry/Stevens geostrata was to increase the estimated slope, from 0.029 to 0.042 per Gy. The statistical significance of the dose-response changed from p = 0.14 to p = 0.065 (Table IX.P-35, row 8).

P.5.e. Analysis of Diffuse Thyroid UDAs in Relation to Alternative Dose Estimates

Using the first alternative dose estimates, the estimated slope B was not significantly greater than zero (0.010 per Gy with Bonferroni-adjusted 95% CI ranging from less than -0.041 to 0.078 per Gy), providing no evidence that prevalence increased with increasing dose (p = 0.34; Table IX.P-35, row 9). Similar results were found with the second set of alternative dose estimates, with an estimated slope of (0.013 per Gy with Bonferroni-adjusted 95% CI ranging from -0.037 to 0.080), and no evidence that the proportion with diffuse thyroid UDAs increased with increasing dose (p = 0.30; Table IX.P-35, row 10).

P.5.f. Scoping Analysis Regarding Out-of-Area Participants

See section VIII.C.1.a.3 for a description of the scoping analyses that were performed to assess the possible impact of the 249 out-of-area participants. The results of both scoping analyses were virtually the same as the primary analysis and provided no evidence that the prevalence of diffuse thyroid UDA increased with increasing dose (Table IX.P-35; rows 11 and 12).

P.5.g. Analysis of Diffuse Thyroid UDAs in Relation to Alternative Representations of Exposure

In the analyses by geostratum and by dichotomous exposure variable, the sex and age-adjusted comparisons of prevalence were performed as described in section VIII.C.2.a.2.

P.5.g.1. Analysis by Geostratum

Among women, the proportions with diffuse thyroid UDAs ranged from 28/131 (21.4%) in the Walla Walla City geostratum to 26/177 (14.7%) in the Richland geostratum (Table IX.P-36). For men they ranged from 11/70 (15.7%) in the Ferry/Stevens geostratum to 9/164 (5.5%) in the Walla Walla County geostratum. The heterogeneity among the nine geostrata was not statistically significant (p = 0.60). Among men diffuse thyroid UDAs were rather more common in the Okanogan and Ferry/Stevens geostrata (14.3%) compared to the other geostrata (8.5%). However among women the proportions were nearly identical (16.8% and 17.7%). The difference between the Okanogan and Ferry/Stevens geostrata versus the other geostrata was not statistically significant (p = 0.32).

Table IX.P-36. Diffuse Ultrasound-Detected Abnormalities, by Geostratum and Sex

	Female			Male			Total		
Geostratum	No.	Cases	%	No.	Cases	%	No.	Cases	%
Richland	177	26	14.7	172	13	7.6	349	39	11.2
Pasco/Kennewick	505	96	19.0	501	40	8.0	1006	136	13.5
Benton County	375	62	16.5	358	39	10.9	733	101	13.8
Franklin County	73	12	16.4	76	10	13.2	149	22	14.8
Adams County	165	32	19.4	156	14	9.0	321	46	14.3
Walla Walla (city)	131	28	21.4	131	8	6.1	262	36	13.7
Walla Walla County	169	26	15.4	164	9	5.5	333	35	10.5
Okanogan County	75	13	17.3	63	8	12.7	138	21	15.2
Ferry/Stevens Counties	68	11	16.2	70	11	15.7	138	22	15.9
Total	1738	306	17.6	1691	152	9.0	3429	458	13.4

P.5.g.2. Analysis by Dichotomous Exposure Variable

Of the 1255 participants included in these analyses, 175 (13.9%) had diffuse thyroid UDA (Table IX.P-37). These included 83/580 (14.3%) in the high exposure group, and 92/675 (13.6%) in the low exposure group. Based on the logistic regression analysis with adjustment for the effect of sex and age at HTDS examination, the proportion of participants with diffuse thyroid UDAs was not significantly elevated in the high exposure group (p = 0.25).

Table IX.P-37. Diffuse Ultrasound-Detected Abnormalities, by Exposure Group and Sex

	Female			Male			Total		
Exposure Group	No.	Cases	%	No.	Cases	%	No.	Cases	%
Low	350	57	16.3	325	35	10.8	675	92	13.6
High	298	58	19.5	282	25	8.9	580	83	14.3
Total	648	115	17.7	607	60	9.9	1255	175	13.9

P.5.h. Confounding and Effect Modification

As described in section VIII above, additional sex-stratified logistic regression models were investigated to examine the possibility that the primary dose-response results might be influenced by confounding, and to search for factors that might modify a radiation dose-response. Table IX.P-38 displays results for models including sex, age at first exposure to Hanford I-131 (prenatal, or < 180 days), age at HTDS examination, estimated dose from the NTS, history of any cancer other than thyroid, and HTDS interview type. Note that sex was not analyzed as a possible confounder since its effect was already adjusted for in the sex-stratified model. It is evident from Table IX.P-38 that the model was not significantly improved by adjusting for any of the other factors as a potential confounder: none produced a significantly better fit to the data. Since the estimated slope was virtually unaffected by such adjustments, it does not appear that omitting these factors introduces any important bias in the dose-response results.

Table IX.P-38. Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other than Thyroid, and Interview Type: Diffuse Ultrasound-Detected Abnormalities

		Estimated Dose-Response Coefficient (per Gy)				
Covariate (0=No, 1=Yes)	Yes / Total	Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
Female?	1614 / 3181	.211 ± .220 (–.317, .738)	Not Applicable	.392 ± .343 (–.464, 1.25)	.095 ± .286 (–.621, .810)	.51
Prenatal exposure?	1031 / 3181	.211 ± .220 (–.317, .738)	.188 ± .223 (–.385, .762)	.364 ± .242 (–.274, 1.00)	–.510 ± .534 (–1.92, .898)	.12
1st exposure before age 180 days?	1474 / 3181	.211 ± .220 (–.317, .738)	.211 ± .223 (–.363, .785)	.254 ± .392 (–.779, 1.29)	.190 ± .273 (–.529, .909)	.89
Age at exam > 50?	1993 / 3181	.211 ± .220 (–.317, .738)	.292 ± .220 (–.275, .859)	.479 ± .359 (–.469, 1.43)	.185 ± .282 (–.559, .928)	.52
NTS I-131 dose > 5.3 mGy?	1563 / 3179	.211 ± .220 (–.316, .739)	.179 ± .226 (–.404, .763)	.358 ± .286 (–.396, 1.11)	–.107 ± .390 (–1.14, .922)	.33
History of any cancer other than thyroid ?	248 / 3176	.220 ± .220 (–.307, .746)	.219 ± .220 (–.348, .785)	.213 ± .244 (–.431, .857)	.243 ± .508 (–1.10, 1.58)	.96
Expanded In-Person Interview?	1205 / 3181	.211 ± .220 (–.317, .738)	.232 ± .224 (–.346, .810)	.450 ± .361 (–.503, 1.40)	.097 ± .296 (–.684, .877)	.45

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Tables IX.P-39 and IX.P-40 display similar results from analyses including history of medical or dental x-ray exposure or occupational exposure as potential confounding or effect modifying factors. There is no evidence of any confounding or statistically significant effect modification.

Table IX.P-39. Confounding and Effect Modification by History of Medical and Dental Radiation Exposures: Diffuse Ultrasound-Detected Abnormalities

		Estimated Dose-Response Coefficient (per Gy)				
Have You Ever Had: (0=No, 1=Yes)	Yes / Total	Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Including Effect Modification Group 1	P
CAT scan of the upper body?	775 / 3139	.195 ± .222 (–.228, .727)	.192 ± .223 (–.381, .766)	.155 ± .247 (–.496, .806)	.376± .539 (–1.04, 1.80)	.71
Diagnostic x-rays of the head?	1188 / 3145	.215 ± .222 (–.316, .745)	.217 ± .221 (–.353, .787)	.242 ± .272 (–.477, .961)	.169 ± .380 (–.834, 1.17)	.88
Diagnostic x-rays of the neck?	960 / 3157	.229 ± .221 (–.299, .757)	.249 ± .221 (–.320, .819)	–.152 ± .325 (–1.01, .705)	.662 ± .304 (–.141, 1.46)	.066
Diagnostic x-rays of chest or upper body, including mammograms?	2811 / 3163	.218 ± .220 (–.309, .745)	.241 ± .220 (–.326, .808)	.563 ± .800 (–1.55, 2.67)	.216 ± .230 (–.390, .822)	.68
Diagnostic x-rays of the stomach or mid-back?	691 / 3110	.247 ± .220 (–.280, .775)	.248 ± .220 (–.319, .816)	.155 ± .254 (–.515, .825)	.578 ± .456 (–.625, 1.78)	.42
Barium enema?	821 / 3149	.183 ± .224 (–.353, .718)	.182 ± .224 (–.395, .758)	.338 ± .252 (–.326, 1.00)	–.312 ± .493 (–1.61, .990)	.22
Upper GI?	1140 / 3167	.204 ± .222 (–.327, .735)	.201 ± .222 (–.370, .773)	.256 ± .275 (–.470, .981)	.105 ± .374 (–.881, 1.09)	.75
Intravenous pyelogram?	396 / 3147	.213 ± .223 (–.321, .746)	.222 ± .223 (–.352, .795)	.143 ± .239 (–.489, .774)	.919 ± .673 (–.855, 2.69)	.29
Fluoroscopy of the upper body?	246 / 3151	.193 ± .223 (–.341, .727)	.196 ± .223 (–.378, .771)	.239 ± .228 (–.363, .840)	–.459 ± .945 (–2.95, 2.03)	.46
Other nuclear scan?	216 / 3152	.239 ± .220 (–.287, .765)	.248 ± .219 (–.318, .813)	.325 ± .220 (–.255, .905)	–2.19 ± 1.53 (–6.22, 1.84)	.063
Dental x-rays that did not usually include a lead shield over the neck area?	1644 / 3181	.211 ± .220 (–.317, .738)	.207 ± .220 (–.361, .775)	.308 ± .309 (–.508, 1.12)	.108 ± .316 (–.726, .942)	.65

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-40. Confounding and Effect Modification by Occupational History: Diffuse Ultrasound-Detected Abnormalities

Have You Ever Worked in Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted Estimate	Incl. Confounding Estimate	Including Effect Modification Group 0	Group 1	P
Any metal industry?	238 / 3181	.211 ± .220 (–.317, .738)	.214 ± .220 (–.354, .782)	.253 ± .223 (–.337, .842)	–.669 ± 1.14 (–3.67, 2.33)	.41
Any nuclear facility?	370 / 3181	.211 ± .220 (–.317, .738)	.195 ± .222 (–.377, .767)	.096 ± .252 (–.568, .760)	.606 ± .479 (–.658, 1.87)	.36
Any other industry or occupation where you may have been exposed to radioactive materials or x-rays?	442 / 3181	.211 ± .220 (–.317, .738)	.219 ± .220 (–.348, .786)	.327 ± .237 (–.299, .953)	–.436 ± .698 (–2.28, 1.41)	.25
Any of the above industries or occupations?	891 / 3181	.211 ± .220 (–.317, .738)	.200 ± .221 (–.370, .770)	.283 ± .266 (–.417, .984)	.023 ± .403 (–1.04, 1.09)	.59

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

Table IX.P-41 displays the results of analyses of possible confounding or effect modification by smoking variables. There was no evidence that the dose-response was significantly confounded by either smoking variable, or that there was a dose-response that differed significantly according to smoking history.

Table IX.P-41. Confounding and Effect Modification by Smoking: Diffuse Ultrasound-Detected Abnormalities

Have You Ever Smoked Any of the Following: (0=No, 1=Yes)	Yes / Total	Estimated Dose-Response Coefficient (per Gy) Unadjusted Estimate	Incl. Confounding. Estimate	Including Effect Modification Group 0	Group 1	P
Cigarettes (unfiltered or filtered)?	1850 / 3173	.218 ± .220 (–.309, .744)	.224 ± .221 (–.344, .792)	.285 ± .366 (–.680, 1.25)	.190 ± .278 (–.545, .924)	.84
Any of cigarettes, cigar or pipe?	1896 / 3173	.218 ± .220 (–.309, .744)	.224 ± .221 (–.345, .793)	.217 ± .370 (–.759, 1.19)	.228 ± .275 (–.497, .953)	.98

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified logistic regression models. P-values indicate the statistical significance of two-tailed comparison of estimated coefficients between Groups 0 and 1.

P.5.i. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for the outcome of diffuse thyroid UDA are shown in Figure IX.P-8 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure are calculated at the 98.33% confidence level, i.e., are adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope is greater than 0 for 88 of the 100 realizations, the confidence interval includes 0 for all but 1 of the realizations. Also shown in Figure IX.P-8 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean and mean of each participant's 100 dose realizations. In summary, for only one of the 100 realizations of the estimated doses was there a statistically significant dose-response, although for most of the realizations the estimated slope was greater than 0.

Figure IX.P-8. Plot of Estimated Slope and 95% CI by Dose Realization: Diffuse Ultrasound-Detected Abnormalities

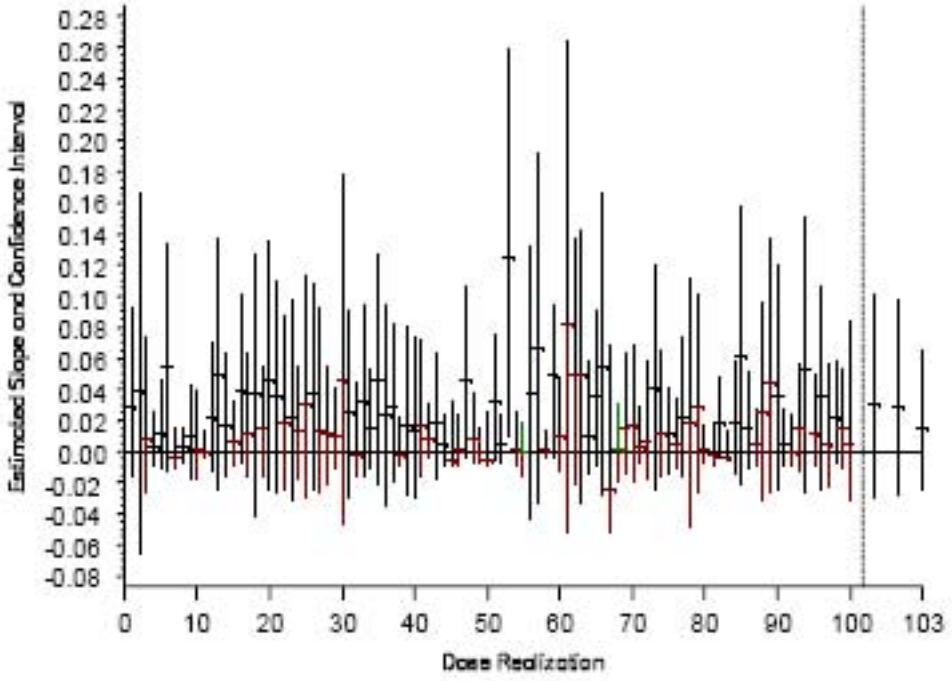
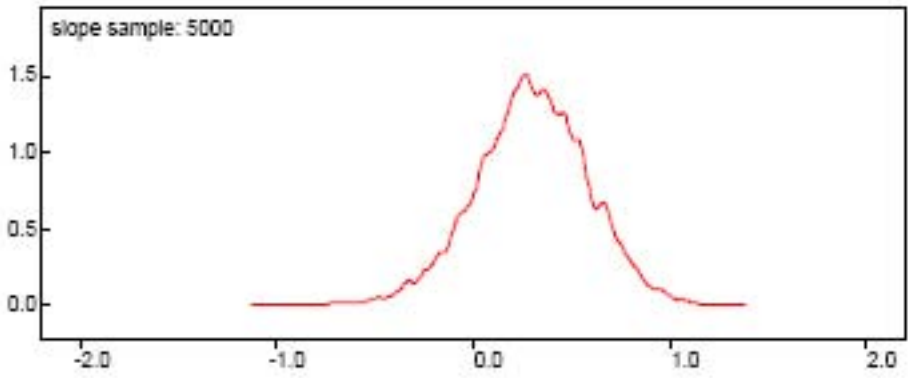


Figure IX.P-9 displays the distribution of the 5000 logistic regression coefficient estimates obtained by the simulation procedures described in section VIII.C.2.b.3 above. It is evident from the figure that most of the estimates were between about –0.5 and 1.0. The estimate was less than or equal to 0 for 713 of the 5000 replications, implying an empirical one-tailed p-value of 0.14. The median estimate was 0.30, and the upper and lower percentiles corresponding to the Bonferroni-adjusted 95% confidence interval were –0.42 and 0.96. These may be compared to the p-value of 0.17 and the estimate of 0.21 with confidence interval (–0.32, 0.74) obtained using the median dose estimates without adjustment for uncertainty. Thus, this method of adjusting the estimated logistic regression coefficient for the uncertainty in the dose estimates did not provide evidence that the prevalence of diffuse thyroid UDA increased with increasing dose.

Figure IX.P-9. Distribution of Simulation Estimates of Logistic Regression Coefficient: Diffuse Ultrasound-Detected Abnormalities



Q. Laboratory Values

Associations between laboratory values and estimated thyroid radiation dose were investigated by fitting the linear dose-response model [4], described in section VIII.C.1.a above. The regression coefficient B in this model plays a role analogous to that in the model [1] for cumulative incidence. In particular the direction and magnitude of each estimated dose-response relationship is represented by the estimate of the regression coefficient. An estimate of B greater than 0 indicates that the mean of the laboratory value tended to increase with increasing dose, while an estimate less than 0 indicates that the mean tended to decrease with increasing dose. The statistical significance of the dose-response was tested using the likelihood ratio statistic.

The p-values used to characterize the statistical significance of associations between lab values and estimated radiation dose were reported for two-tailed tests. This differed from the use of one-sided p-values in the tests for association with disease outcomes.

Of the 3191 living evaluable in-area participants, 3183 (99.7%) consented to provide a blood specimen at their HTDS clinic.

Q.1. Thyroid Stimulating Hormone (TSH)

Of the 3183 living evaluable in-area participants who provided blood samples, 222 were receiving exogenous thyroid hormone at the time of their HTDS clinic. These 222 were excluded from the analyses of TSH levels. Among the remaining 2961 living evaluable participants, 584 had TSH measured by RIA, 810 by EIA-1, and 1567 by EIA-2. Table IX.Q-1 displays the minimum, maximum, and median TSH levels of the 584 participants for whom RIA was used.

Table IX.Q-1. Distributions of TSH Levels Measured by RIA, by Sex

	TSH (μIU/ml) measured by RIA		
	Female (N = 281)	Male (N = 303)	Total (N = 584)
Minimum	0.1	0.3	0.1
Maximum	52.9	100.0	100.0
Median	2.3	2.3	2.3

Tables IX.Q-2 and IX.Q-3 display similar results for the participants whose TSH levels were measured by either of the two EIA assays. For two participants with TSH measured by EIA-1 and six with TSH measured by EIA-2, the TSH levels were reported simply as < 0.03 μIU/ml and < 0.04 μIU/ml, respectively. Such measurements are “left-censored”, that is, their specific values are not known, and they are known only to be less than the specified value.

Table IX.Q-2. Distributions of TSH Levels Measured by EIA-1, by Sex

	TSH (μIU/ml) measured by EIA-1		
	Female (N = 376)	Male (N = 434)	Total (N = 810)
Minimum	< 0.03	0.21	< 0.03
Maximum	50.34	28.77	50.34
Median	1.59	1.37	1.49
Number (%) below lower measurement limit (< 0.03 μIU/ml)	2 (0.5%)	0 (0%)	2 (0.2%)

Table IX.Q-3. Distributions of TSH Levels Measured by EIA-2, by Sex

	TSH (μIU/ml) measured by EIA-2		
	Female (N = 766)	Male (N = 801)	Total (N = 1567)
Minimum	< 0.04	< 0.04	< 0.04
Maximum	24.12	22.46	24.12
Median	1.49	1.22	1.35
Number (%) below lower measurement limit (< 0.04 μIU/ml)	5 (0.7%)	1 (0.1%)	6 (0.4%)

It is evident from Tables IX.Q-1 through IX.Q-3 above that the distributions of TSH values were quite skewed to the right, since the median values are much closer to the minima than the maxima. Therefore the regression model was applied to the logarithms of the TSH values. Figures IX.Q-1 through IX.Q.3 display the TSH values, plotted on the logarithmic scale, in relation to estimated thyroid radiation dose.

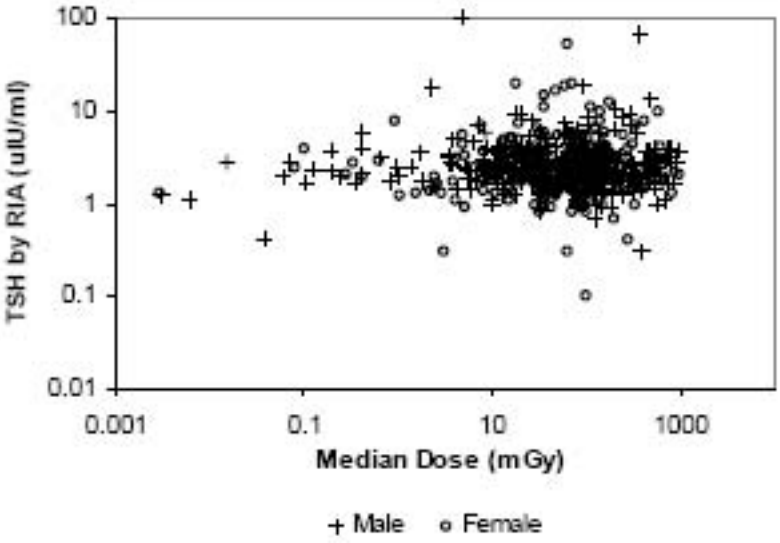


Figure IX.Q-1. Scatter Plot of TSH by RIA and Estimated Dose

Figure IX.Q-2. Scatter Plot of TSH by EIA-1 and Estimated Dose

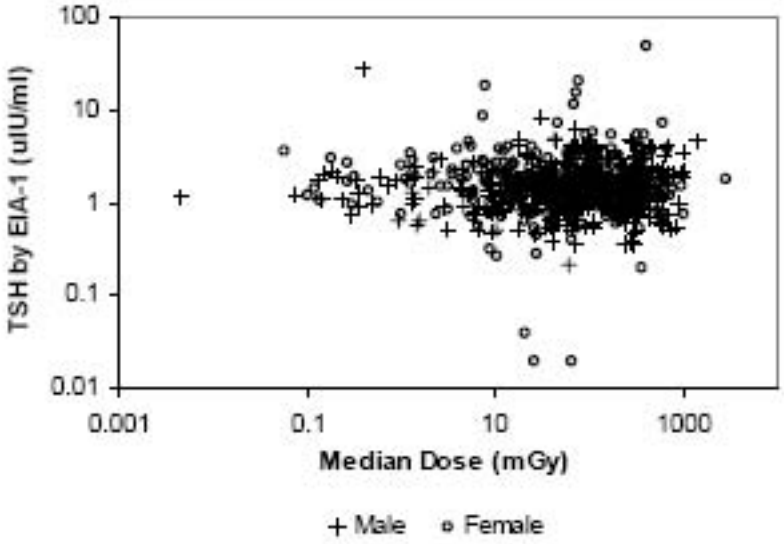
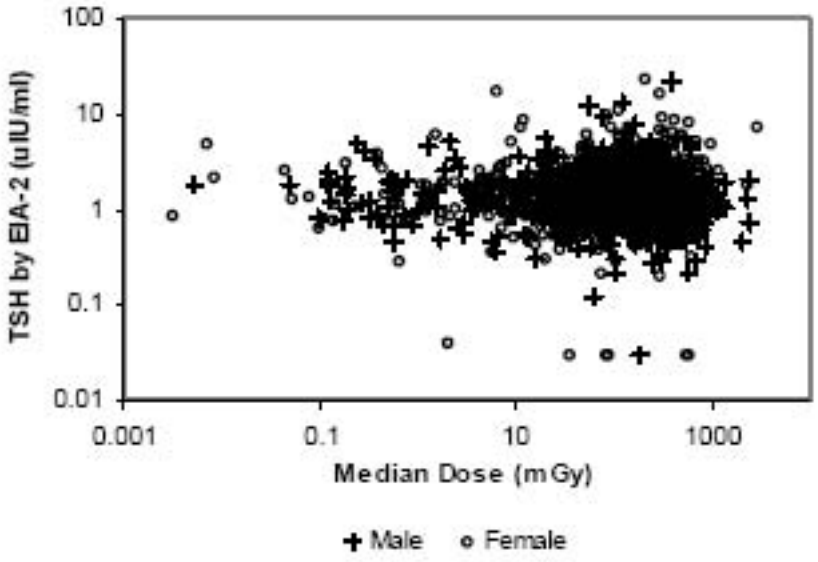


Figure IX.Q-3. Scatter Plot of TSH by EIA-2 and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log(TSH) are summarized for the three types of assays in Table IX.Q-4 below. In the table, parameter estimates are converted from the scale of log(TSH) back to TSH. So, for example, the estimated average RIA-based TSH for women of 2.45 μIU/ml is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy. For example, the estimated average (geometric mean) TSH level for women based on EIA-1 increased from 1.58 μIU/ml at 0 Gy to $1.58 \times 1.142^2 = 2.06$ μIU/ml at 2 Gy (2000 mGy). For none of the three assays was there a significant trend in relation to estimated radiation dose.

Table IX.Q-4. Parameter Estimates for Dose-Response Models: TSH

Parameter	RIA (μIU/ml)	EIA – 1 (μIU/ml)	EIA – 2 (μIU/ml)
No. of living evaluable participants	584	810	1567
No. with left-censored values	0	2	6
Estimated average background TSH for women	2.45 (2.22, 2.71)	1.58 (1.45, 1.72)	1.48 (1.39, 1.57)
Estimated average background TSH for men	2.43 (2.20, 2.68)	1.36 (1.26, 1.48)	1.26 (1.18, 1.34)
Estimated percentage change in average TSH per Gy	+2.0% (–30.0%, +48.9%)	+14.2% (–12.0%, +48.0%)	+1.5% (–12.2%, +17.2%)
Statistical significance of dose-response (two-tailed p-value)	0.90	0.22	0.82

Entries in the table for model parameters are the parameter estimate, with Bonferroni-adjusted 95% confidence interval in parentheses, based on sex-stratified linear model for log (TSH).

Since the average levels of TSH differed rather substantially among the three assays, it was not considered appropriate to simply combine all three groups and attempt to fit the simple sex-stratified linear regression model [4]. Therefore a generalization of the sex-stratified linear model was examined, in which the mean values of log(TSH) were assumed to differ between the sexes and according to the type of assay. When this model was fit to the data for all 2961 living evaluable participants with TSH measurements, there was still no significant trend of average log(TSH) in relation to estimated thyroid radiation dose. If a common slope was assumed for all three assays, the estimated regression coefficient was +4.5% per Gy with Bonferroni-adjusted 95% confidence limits −8.4% and +19.1% per Gy, which was not significantly different from zero (two-tailed $p = 0.42$).

Q.1.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log (TSH) by RIA, EIA-1, and EIA-2 are shown in Figures IX.Q-4 through IX.Q-6 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in these figures were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. The point estimate of the slope was greater than 0 for 59, 94, and 65 of the 100 realizations for TSH by RIA, EIA-1, and EIA-2, respectively. However the confidence intervals included 0 for all 100 realizations for TSH by RIA and EIA-2, and for 96 of the 100 realizations for EIA-1.

Also shown in Figures IX.Q-4 through IX.Q-6 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-4. Estimated Dose-Response for TSH by RIA, by Dose Realization

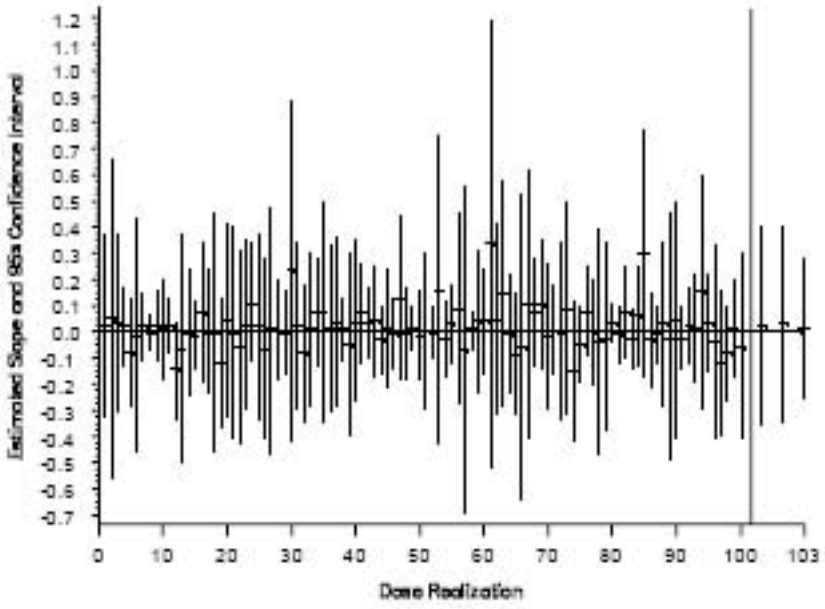


Figure IX.Q-5. Estimated Dose-Response for TSH by EIA-1, by Dose Realization

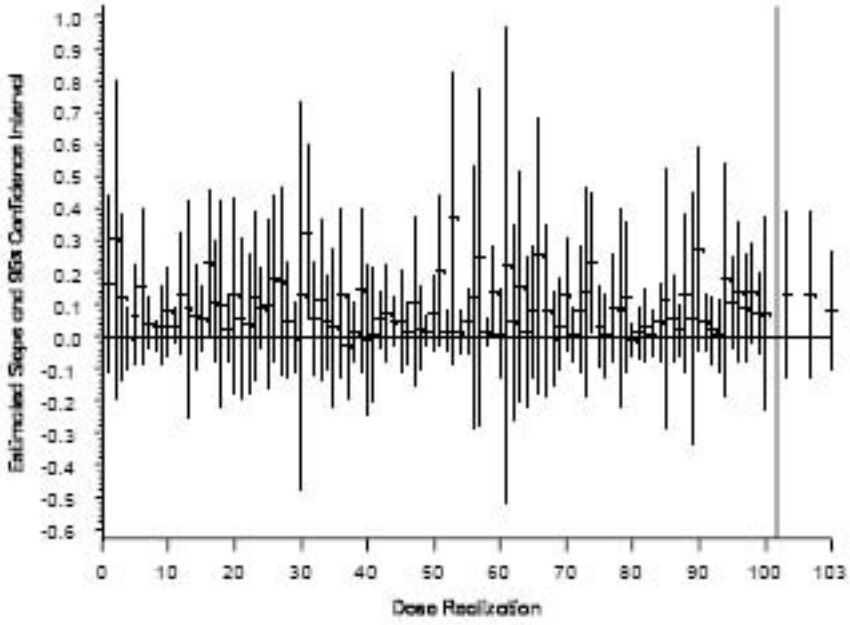
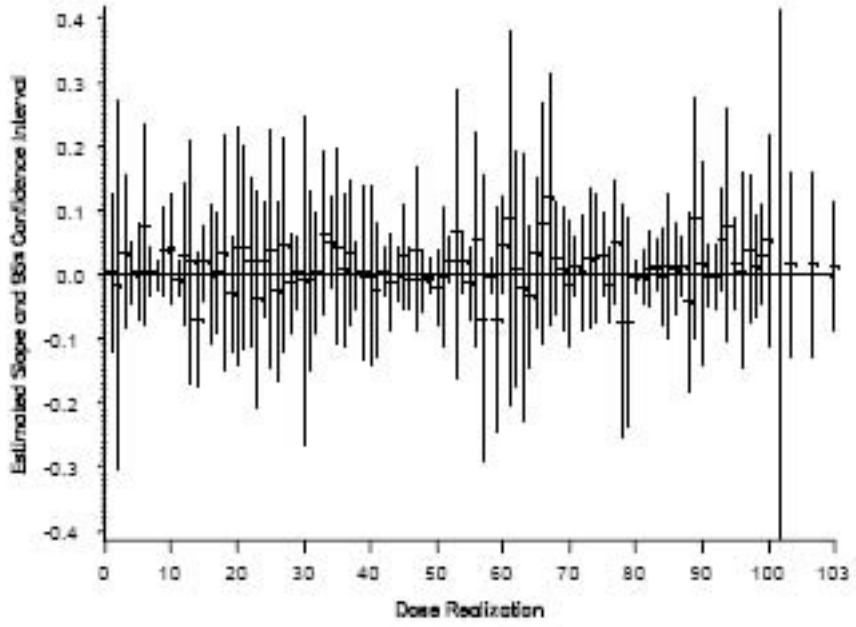


Figure IX.Q-6. Estimated Dose-Response for TSH by EIA-2, by Dose Realization



Q.2. Total Thyroxine (T4)

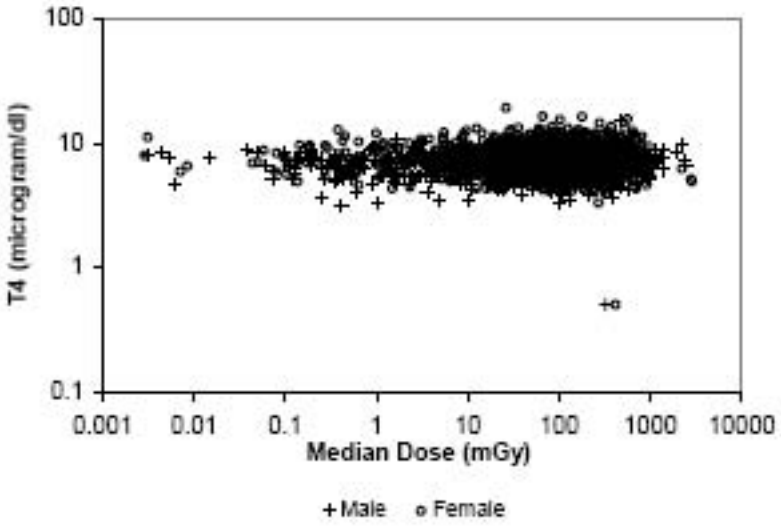
The 222 living evaluable in-area participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic were excluded from the primary analysis of T4. The T4 values were unknown for two additional in-area participants due to insufficient volumes of collected blood. Table IX.Q-5 displays the minimum, maximum, and median T4 levels of the 2959 participants for whom data were available. For two of these participants the T4 levels were left censored, reported as < 1.0 μg/dl. All other T4 levels were 3.1 μg/dl or greater. Therefore the distribution of T4 levels was somewhat skewed to the right, and consequently the regression model was applied to the logarithms of the T4 values.

Table IX.Q-5. Distributions of Total Thyroxine (T4) Levels, by Sex

	T4 (μg/dl)		
	Female (N = 1422)	Male (N = 1537)	Total (N = 2959)
Minimum	< 1.0	< 1.0	< 1.0
Maximum	19.1	15.2	19.1
Median	7.5	6.6	7.0
Number (%) below lower measurement limit (< 1.0 μg/dl)	1 (0.07%)	1 (0.07%)	2 (0.07%)

T4 values, plotted on the logarithmic scale, are shown by estimated dose in Figure IX.Q-7.

Figure IX.Q-7. Scatter Plot of T4 and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log(T4) are summarized in Table IX.Q-6 below. In the table, parameter estimates are converted from the scale of log(T4) back to T4. So, for example, the estimated average T4 of 7.52 μg/dl for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy. For example, the estimated average (geometric mean) T4 level for women decreased from 7.52 μg/dl at 0 Gy to $7.52 \times 0.996^2 = 7.46$ μg/dl at 2 Gy (2000 mGy). There was no significant trend of T4 in relation to estimated radiation dose (two-tailed p = 0.84).

Table IX.Q-6. Parameter Estimates for Dose-Response Models: T4

Parameter	T4 (μg/dl)
No. of living evaluable participants	2959
No. with left-censored values	2
Estimated average background T4 for women	7.52 (7.41, 7.64)
Estimated average background T4 for men	6.58 (6.48, 6.67)
Estimated percentage change in average T4 per Gy	–0.4% (–4.5%, +4.0%)
Statistical significance of dose-response (two-tailed p-value)	0.84

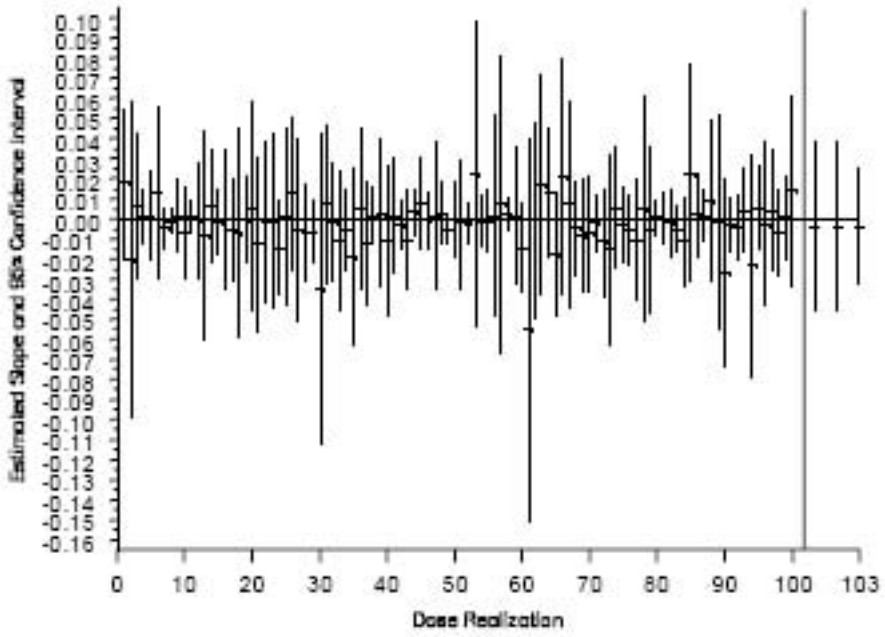
Entries for model parameters (background means and slope) in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.2.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log of T4 are shown in

Figure IX.Q-8 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 42 of the 100 realizations, the confidence interval included 0 for all of the 100 realizations. Also shown in Figure IX.Q-8 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-8. Estimated Dose-Response for T4, by Dose Realization



Q.3. Triiodothyronine Resin Uptake (T3RU)

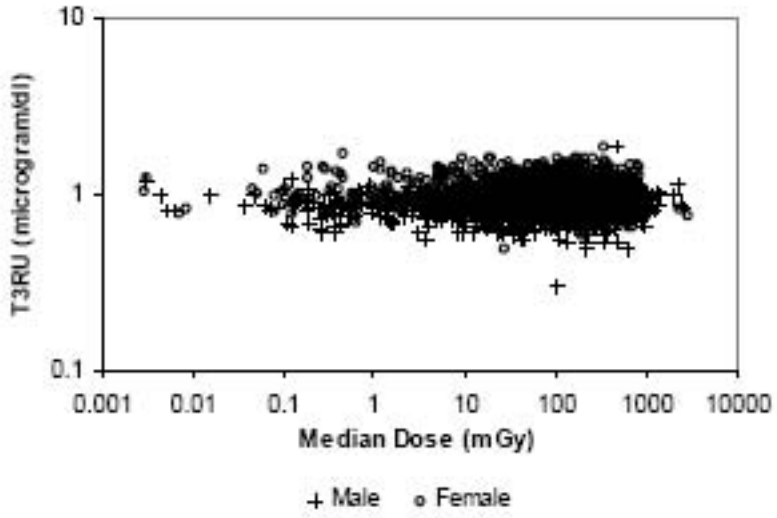
The 222 living evaluable in-area participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic were excluded from the analyses of T3RU. The T3RU values were unknown for two additional in-area participants, the same two whose T4 values were unknown due to insufficient volumes of collected blood. Table IX.Q-7 displays the minimum, maximum, and median T3RU levels of the 2959 participants for whom data were available. For one of these participants the T3RU level was left censored, reported as < 0.4 μg/dl. All other T3RU levels were 0.49 μg/dl or greater. The distribution of T3RU levels was somewhat skewed to the right, and therefore the regression model was applied to the logarithms of the T3RU values.

Table IX.Q-7. Distributions of T3 Resin Uptake (T3RU), by Sex

	T3RU (μg/dl) Female (N = 1422)	Male (N = 1537)	Total (N = 2959)
Minimum	0.49	< 0.4	< 0.4
Maximum	1.87	1.86	1.87
Median	1.00	0.86	0.92
Number (%) below lower measurement limit (< 0.4)	0 (0%)	1 (0.1%)	1 (0.03%)

T3RU values, plotted on the logarithmic scale, are shown by estimated dose in Figure IX.Q-9.

Figure IX.Q-9. Scatter Plot of T3RU and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log(T3RU) are summarized in Table IX.Q-8 below. In the table, parameter estimates are converted from the scale of log(T3RU) back to T3RU. So, for example, the estimated average T3RU of 1.02 μg/dl for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy. For example, the estimated average (geometric mean) T3RU level for women decreased from 1.02 μg/dl at 0 Gy to $1.02 \times 0.988^2 = 1.00$ μg/dl at 2 Gy (2000 mGy). There was no significant trend of T3RU in relation to estimated radiation dose (two-tailed p = 0.36).

Table IX.Q-8. Parameter Estimates for Dose-Response Models: T3RU

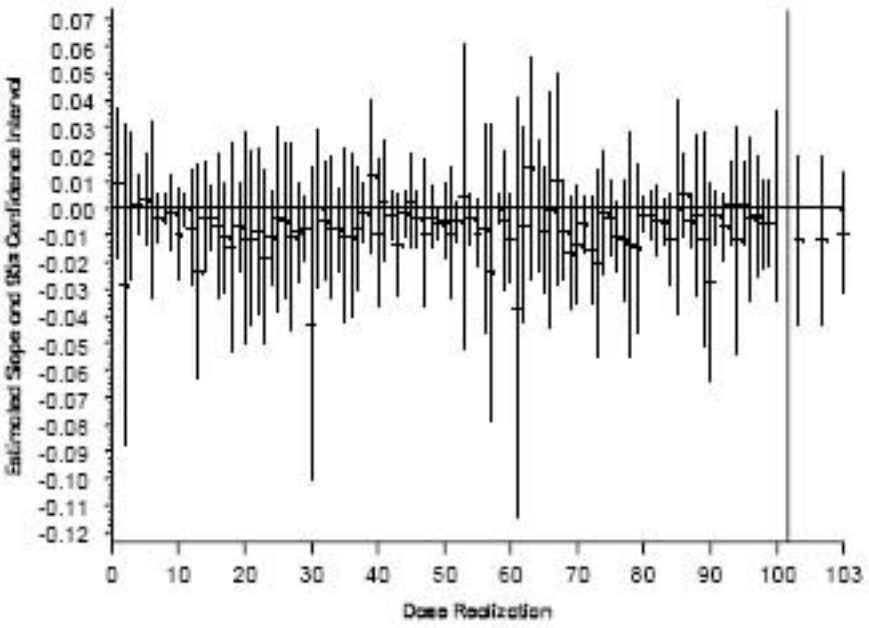
Parameter	T3RU (μg/dl)
No. of living evaluable participants	2959
No. with left-censored values	1
Estimated average background T3RU for women	1.02 (1.01, 1.03)
Estimated average background T3RU for men	0.85 (0.84, 0.86)
Estimated percentage change in average T3RU per Gy	–1.2% (–4.3%, +2.0%)
Statistical significance of dose-response (two-tailed p-value)	0.36

Entries for model parameters (background means and slope) in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.3.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log of T3RU values are shown in Figure IX.Q-10 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 15 of the 100 realizations, the confidence interval included 0 for all of the 100 realizations. Also shown in Figure IX.Q-10 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-10. Estimated Dose-Response for T3RU, by Dose Realization



Q.4. Free Thyroxine Index (FTI)

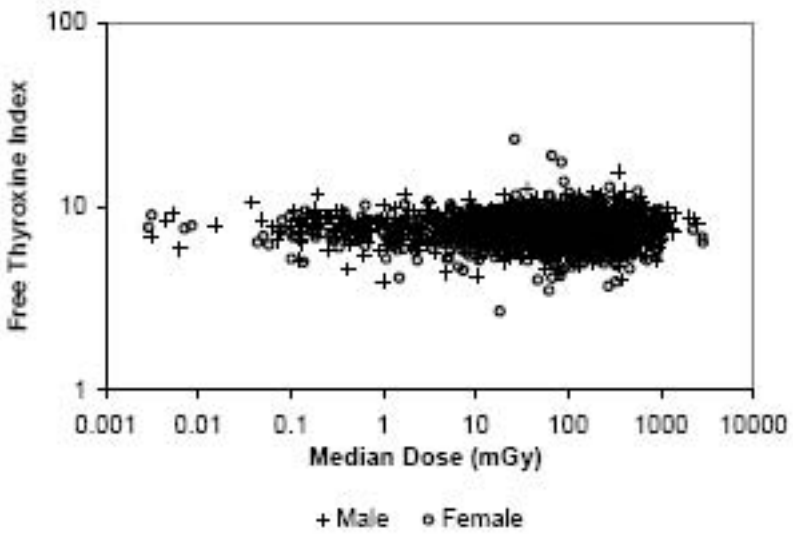
The 222 living evaluable in-area participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic were excluded from the primary analyses of FTI. The FTI values were unknown for five additional in-area participants: the two with unknown T4 and T3RU, and three others for whom either T4 or T3RU was below its level of detection. Table IX.Q-9 displays the minimum, maximum, and median FTI values of the 2956 participants for whom data were available. Since the distribution of FTI values was somewhat skewed to the right, regression modeling of the dose-response was applied to the logarithms of the FTI values.

Table IX.Q-9. Distributions of Free Thyroxine Index (FTI), by Sex

	FTI		
	Female (N = 1421)	Male (N = 1535)	Total (N = 2956)
Minimum	2.7	3.9	2.7
Maximum	23.3	15.4	23.3
Median	7.4	7.8	7.6

FTI values, plotted on the logarithmic scale, are shown by estimated dose in Figure IX.Q-11.

Figure IX.Q-11. Scatter Plot of FTI and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log(FTI) are summarized in Table IX.Q-10 below. In the table, parameter estimates are converted from the scale of log(FTI) back to FTI. So, for example, the estimated average FTI of 7.38 for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy. For example, the estimated average (geometric mean) FTI level for women increased from 7.38 at 0 Gy to $7.38 \times 1.016^2 = 7.62$ at 2 Gy (2000 mGy). There was no significant trend of FTI in relation to estimated radiation dose (two-tailed $p = 0.23$).

Table IX.Q-10. Parameter Estimates for Dose-Response Models: FTI

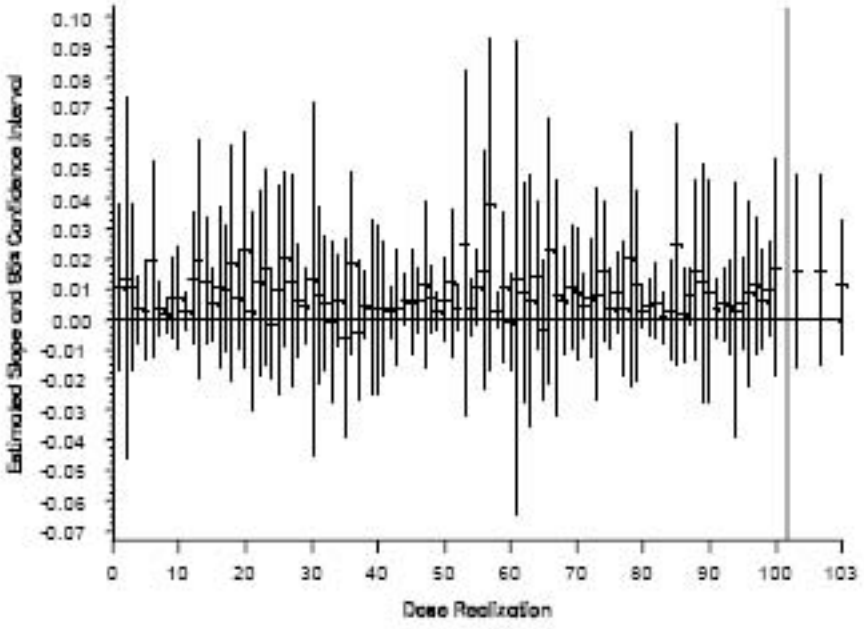
Parameter	FTI
No. of living evaluable participants	2956
Estimated average background FTI for women	7.38 (7.29, 7.46)
Estimated average background FTI for men	7.72 (7.63, 7.81)
Estimated percentage change in average FTI per Gy	+1.6% (−1.6%, +4.9%)
Statistical significance of dose-response (two-tailed p-value)	0.23

Entries for model parameters (background means and slope) in the tableare estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.4.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log of FTI are shown in Figure IX.Q-12 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 94 of the 100 realizations, the confidence interval included 0 for all of the 100 realizations. Also shown in Figure IX.Q-12 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-12. Estimated Dose-Response for FTI, by Dose Realization



Q.5. Anti-Thyroid Autoimmune Response

Anti-TPO or AMA values were used to measure the anti-thyroid autoimmune responses of 1562 and 1620 in-area living evaluable participants, respectively. Neither assay result was available for eight participants who declined to provide a blood sample, and for one other whose sample was of insufficient volume. Tables IX.Q-11 and IX.Q-12 display the minimum, maximum, and median anti-TPO or AMA values of the participants for whom data were available. For both assays, the majority of participants had values below the lower measurement limits: 80% with anti-TPO < 2.0 IU/ml, and 78% with AMA < 20 IU/ml. In addition, 6% of the participants assayed by AMA had values above the upper measurement limit, i.e., > 700 U/ml. Since the distributions of these values were skewed to the right, they were log-transformed for regression modeling of the dose-responses.

Table IX.Q-11. Distributions of Anti-TPO, by Sex

	Anti-TPO (IU/ml)		
	Female (N = 812)	Male (N = 750)	Total (N = 1562)
Minimum	< 2.0	< 2.0	< 2.0
Maximum	9569.7	1631.7	9569.7
Median	< 2.0	< 2.0	< 2.0
Number (%) below lower measurement limit (< 2.0 IU/ml)	594 (73%)	651 (87%)	1245 (80%)

Table IX.Q-12. Distributions of AMA, by Sex

	AMA (U/ml)		
	Female (N = 803)	Male (N = 817)	Total (N = 1620)
Minimum	< 20	< 20	< 20
Maximum	> 700	> 700	> 700
Median	< 20	< 20	< 20
Number (%) below lower measurement limit (< 20 U/ml)	590 (73%)	674 (82%)	1264 (78%)
Number (%) above upper measurement limit (> 700 U/ml)	63 (8%)	30 (4%)	93 (6%)

Anti-TPO and AMA results, plotted on logarithmic scales, are shown by estimated dose in Figures IX.Q-13 and IX.Q-14.

Figure IX.Q-13. Scatter Plot of Anti-TPO and Estimated Dose

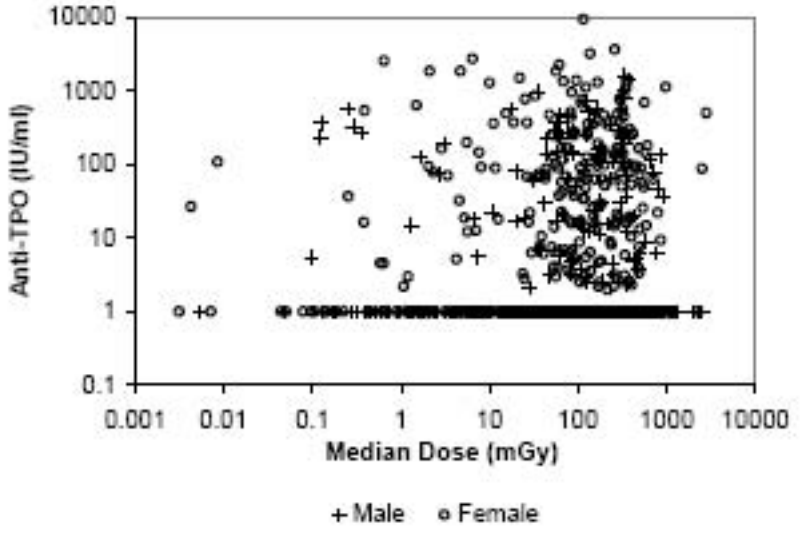
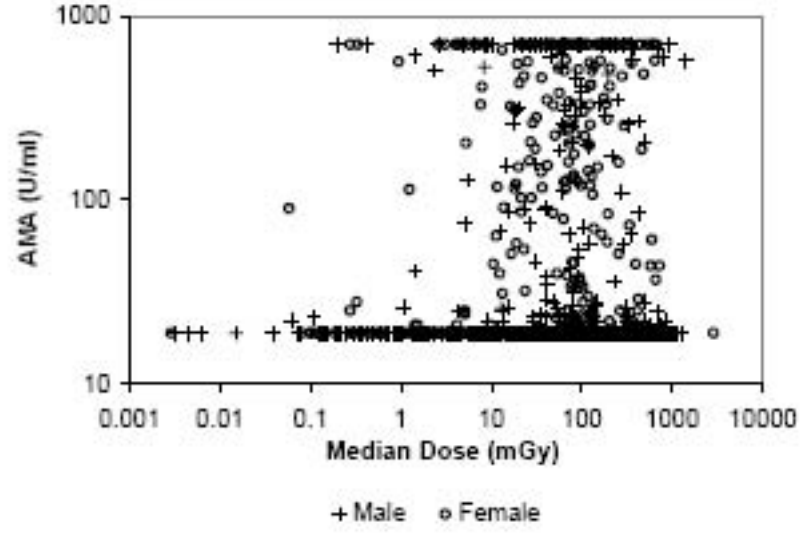


Figure IX.Q-14. Scatter Plot of AMA and Estimated Dose



The results of fitting the sex-stratified linear dose-response models for log(anti-TPO) and log(AMA) are summarized in Table IX.Q-13 below. In the table, parameter estimates are converted from the scales of logarithmically transformed values back to the original scales. So, for example, the estimated average anti-TPO of 0.03 IU/ml for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy, with estimates less than zero indicating that the assay value decreased with increasing estimated thyroid dose. Since the majority of participants had anti-TPO or AMA values below their respective lower limits of measurement, the estimated parameter values have little meaning. Nevertheless these regression results provide no evidence that either value tended to increase sharply with increasing estimated dose (two-tailed p = 0.66 for anti-TPO, p = 0.52 for AMA).

Table IX.Q-13. Parameter Estimates for Dose-Response Models: Anti-TPO and AMA

Parameter	Anti-TPO (IU/ml)	AMA (U/ml)
No. of living evaluable participants	1562	1620
No. with left-censored values	1245	1264
No. with right-censored values	0	93
Estimated average background for women	0.03 (0.01, 0.07)	1.30 (0.63, 2.68)
Estimated average background for men	0.001 (0.000, 0.005)	0.29 (0.12, 0.70)
Estimated percentage change in average per Gy	–32.1% (–91.7%, +453%)	–39.9% (–91.2%, +312%)
Statistical significance of dose-response (two-tailed p-value)	0.66	0.52

Entries for model parameters (background means and slope) in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.5.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response models for log of Anti-TPO and log of AMA are shown in Figures IX.Q-15 and IX.Q-16 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in these figures were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 30 of the 100 realizations for anti-TPO and for 18 realizations for AMA, the confidence intervals for both assays included 0 for all of the 100 dose realizations. Also shown in Figures IX.Q-15 and IX.Q-16 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-15. Estimated Dose-Response for Anti-TPO, by Dose Realization

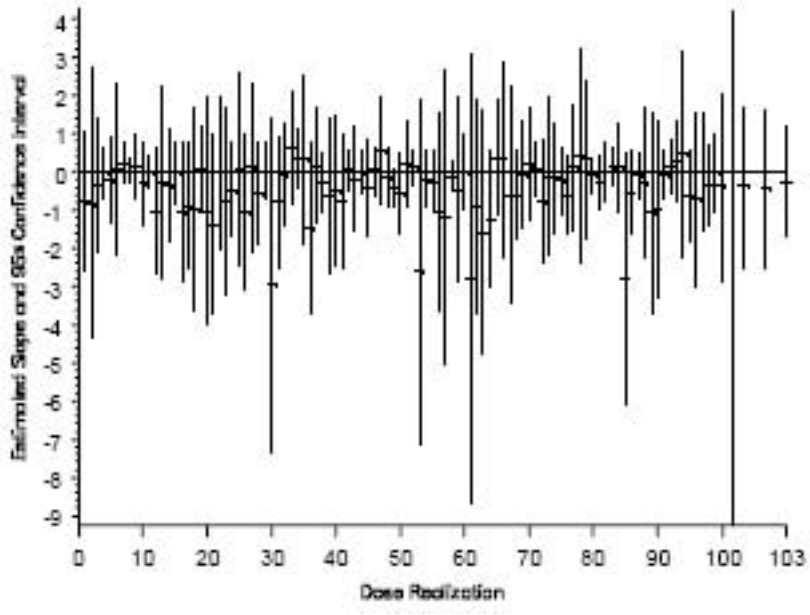
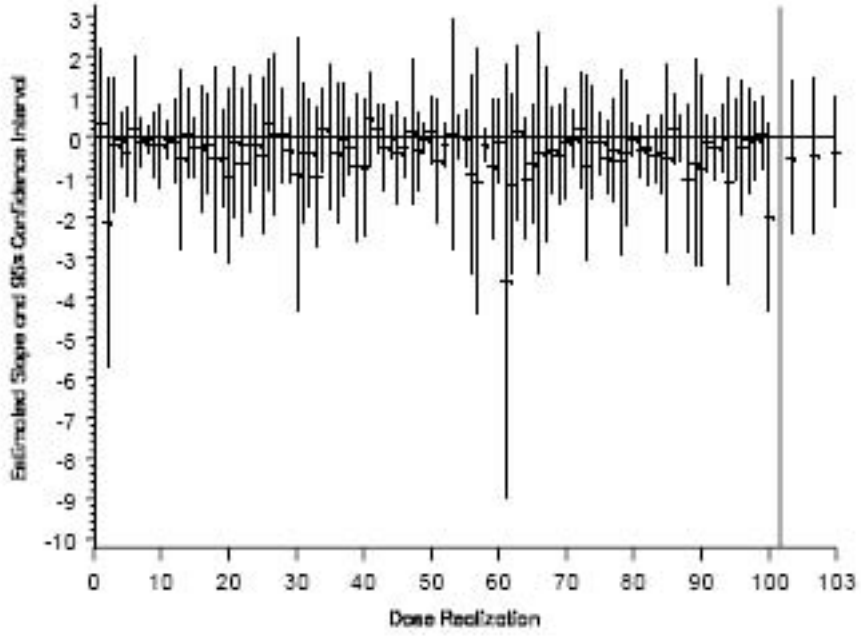


Figure IX.Q-16. Estimated Dose-Response for AMA, by Dose Realization



Q.6. Anti-Thyroglobulin Antibody (anti-TG)

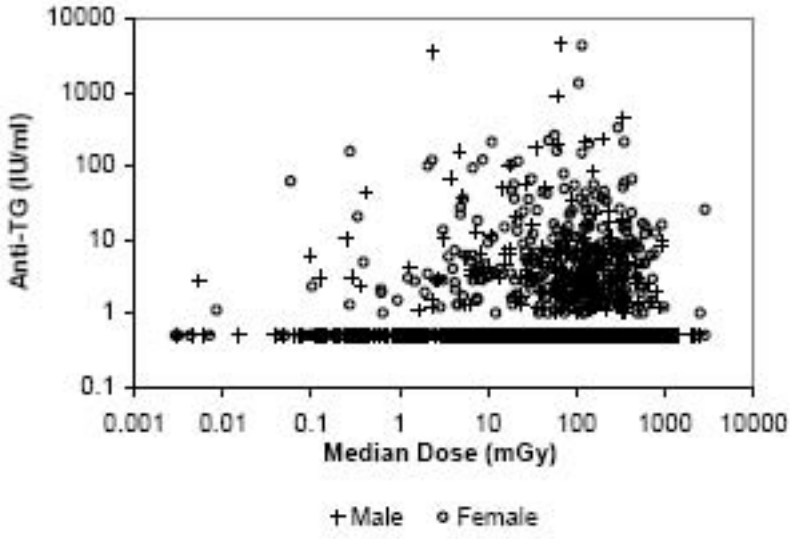
Anti-TG values were not available for 13 of the 3183 living evaluable in area participants who provided blood specimens due to insufficient volume and broken tubes. Table IX.Q-14 displays the minimum, maximum, and median anti-TG values of the 3170 participants for whom data were available. The lower limit of measurement for anti-TG was 1.0 IU/ml, and the majority of participants (85%) had values reported as < 1.0 IU/ml. Since the distribution of anti-TG values was skewed to the right, regression modeling of the dose-response was applied to the logarithms of the anti-TG values.

Table IX.Q-14. Distributions of Anti-TG, by Sex

	Anti-TG (IU/ml)		
	Female (N = 1607)	Male (N = 1563)	Total (N = 3170)
Minimum	< 1.0	< 1.0	< 1.0
Maximum	4300	4500	4500
Median	< 1.0	< 1.0	< 1.0
Number (%) below lower measurement limit (< 1.0 IU/ml)	1281 (80%)	1400 (90%)	2681 (85%)

Anti-TG values, plotted on a logarithmic scale, are shown by estimated dose in Figure IX.Q-17. For clarity, the 2681 values that were below the lower measurement limit of 1.0 IU/ml are plotted at 0.5 IU/ml.

Figure IX.Q-17. Scatter Plot of Anti-TG and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log(anti-TG) are summarized in Table IX.Q-15 below. In the table, parameter estimates are converted from the scale of log(anti-TG) back to anti-TG. So, for example, the estimated average anti-TG of 0.02 IU/ml for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage

change per Gy, with the estimate less than zero indicating that the average anti-TG level decreased with increasing estimated thyroid dose. Since the majority of participants had anti-TG values below the lower limit of measurement, the estimated parameter values have little meaning. Nevertheless these regression results provide no evidence that average anti-TG levels tended to increase sharply with increasing estimated dose (two-tailed p = 0.20).

Table IX.Q-15. Parameter Estimates for Dose-Response Models: Anti-TG

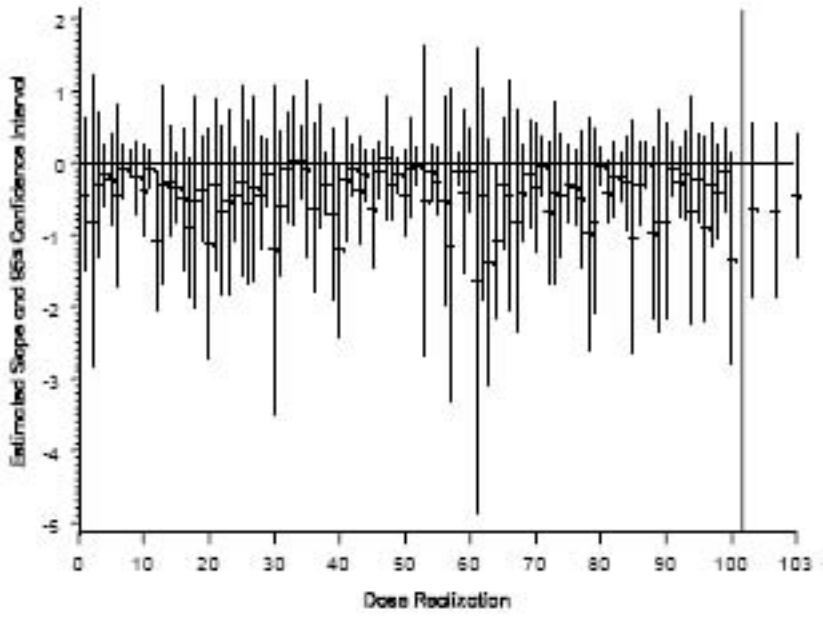
Parameter	Anti-TG (IU/ml)
No. of living evaluable participants	3170
No. with left-censored values	2681
Estimated average background anti-TG for women	0.02 (0.01, 0.03)
Estimated average background anti-TG for men	0.003 (0.002, 0.007)
Estimated percentage change in anti-TG Average per Gy	–47.3% (–84.2%, +75.5%)
Statistical significance of dose-response (two-tailed p-value)	0.20

Entries for model parameters (background means and slope) in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.6.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log of anti-TG are shown in Figure IX.Q-18 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 3 of the 100 realizations, the confidence interval included 0 for 97 of the 100 realizations. Also shown in Figure IX.Q-18 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-18. Estimated Dose-Response for Anti-TG, by Dose Realization



Q.7. Serum Calcium

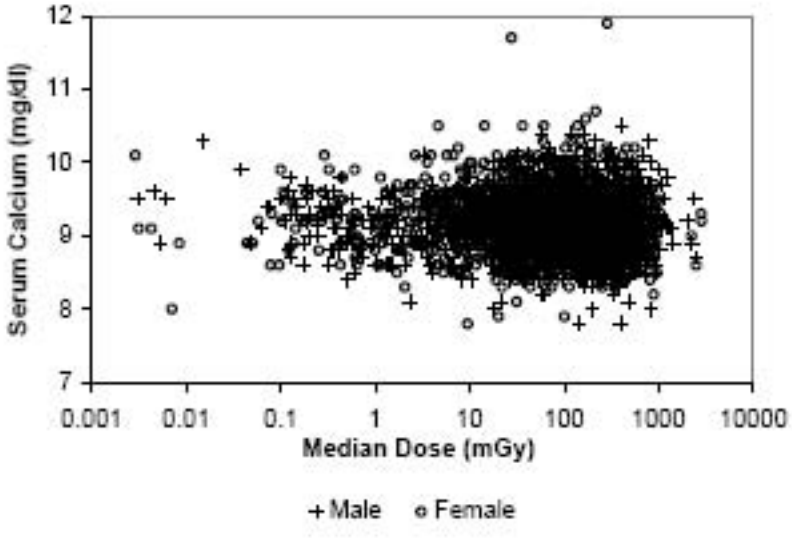
Of the 3183 living evaluable in-area participants who provided blood samples, 227 with diagnoses of hypothyroidism or hyperthyroidism based on the HTDS examination were excluded from the primary analysis of serum calcium levels. Two additional participants did not have serum calcium data due to insufficient volumes of collected blood. Table IX.Q-16 displays the minimum, maximum, and median serum calcium levels of the 2954 participants for whom data were available.

Table IX.Q-16. Distributions of Serum Calcium, by Sex

	Serum Calcium (mg/dl)		
	Female (N = 1448)	Male (N = 1506)	Total (N = 2954)
Minimum	7.8	7.8	7.8
Maximum	11.7	10.5	11.7
Median	9.1	9.2	9.2

Serum calcium levels are shown by estimated dose in Figure IX.Q-19.

Figure IX.Q-19. Scatter Plot of Serum Calcium and Estimated Dose



As can be seen in Figure IX.Q-19, the overall distribution of serum calcium levels was fairly symmetrically distributed, therefore the sex-stratified linear dose-response model [4] was fit without logarithmic transformation. The results are summarized in Table IX.Q-17 below. There was a statistically significant trend of decreasing serum calcium level in relation to increasing radiation dose ($p = 0.0074$). The estimated background means were 9.17 mg/dl for female and 9.19 mg/dl for male, with Bonferroni-adjusted 95% confidence intervals (9.14, 9.20) and (9.16, 9.22), respectively. The estimated slope of the dose-response was –0.09 mg/dl per Gy, with confidence interval ranging from –0.16 to –0.01 mg/dl per Gy, implying that the mean decreased by an average of 0.09 mg/dl with each incremental dose of 1 Gy (1000 mGy). Although this trend is statistically significant, it is small enough in magnitude that the average serum calcium levels remain within the normal range of 8.4 – 10.2 mg/dl. For example, at 3 Gy (3000 mGy), which is larger than the largest dose estimate of any study participant, the average serum calcium level predicted by the regression model for female is $9.17 - 0.09 \times 3 = 8.90$ mg/dl.

Table IX.Q-17. Parameter Estimates for Linear Dose-Response Models: Serum Calcium

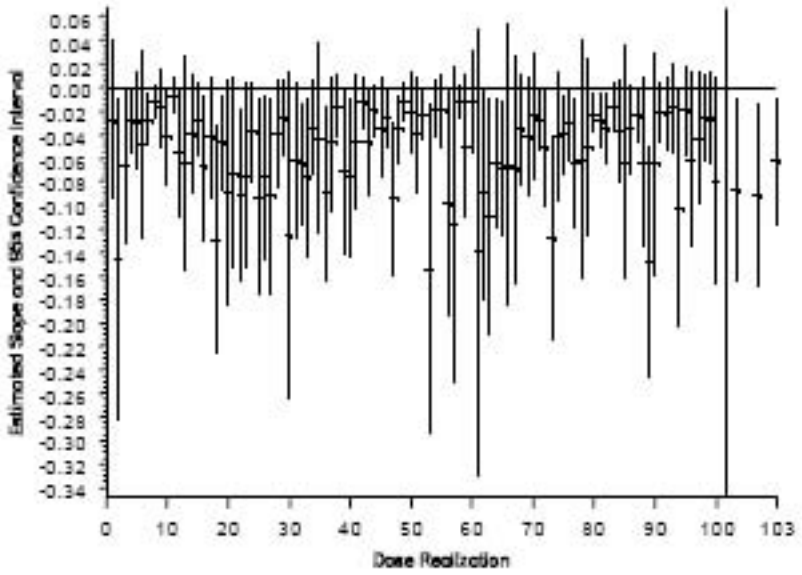
Parameter	Serum Calcium (mg/dl)
No. of living evaluable participants	2954
Estimated average background serum calcium for women	9.17 ± .01 (9.14, 9.20)
Estimated average background serum calcium for men	9.19 ± .01 (9.16, 9.22)
Estimated slope of dose-response (per Gy)	–.09 ± .03 (-.16, -.01)
Statistical significance of dose-response (two-tailed p-value)	0.0074

Entries for model parameters (background means and slope) in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.7.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for serum calcium are shown in Figure IX.Q-20 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was less than 0 for all 100 realizations, the confidence interval included 0 for 61 of the 100 realizations. Also shown in Figure IX.Q-20 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-20. Estimated Dose-Response for Serum Calcium, by Dose Realization



Q.8. Thyroid Mass

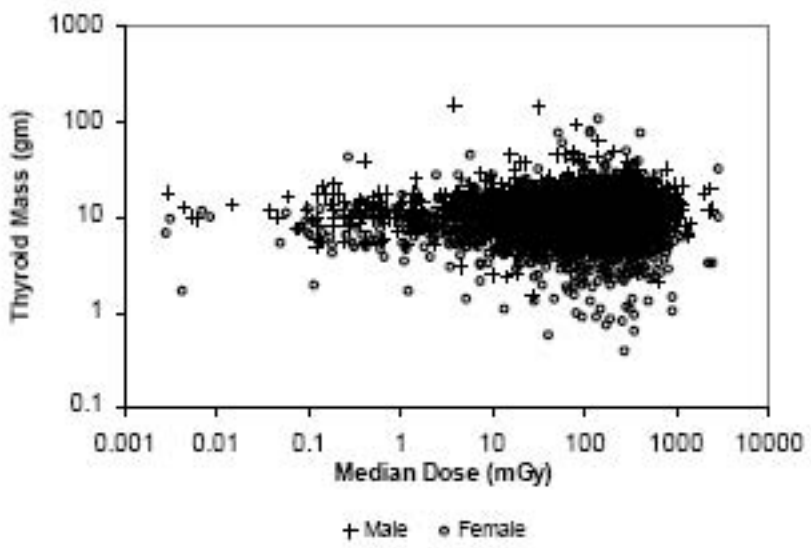
Estimates of thyroid mass were available for 3153 were in-area participants. Table IX.Q-18 displays the minimum, maximum, and median estimates of thyroid mass of these 3153 participants.

Table IX.Q-18. Distributions of Estimated Thyroid Mass, by Sex

	Thyroid Mass (gm)		
	Female (N = 1592)	Male (N = 1561)	Total (N = 3153)
Minimum	0.39	1.53	0.39
Maximum	108.62	149.78	149.78
Median	7.81	11.4	9.53

Thyroid mass, plotted on the logarithmic scale, is shown by estimated dose in Figure IX.Q-21 for these 3153 living evaluable in-area participants.

Figure IX.Q-21. Scatter Plot of Estimated Thyroid Mass and Estimated Dose



The results of fitting the sex-stratified linear dose-response model for log-transformed values of thyroid mass are summarized in Table IX.Q-19 below. In the table, parameter estimates are converted from the logarithmically transformed scale back to the scale of thyroid mass in grams. So, for example, the estimated average thyroid mass of 7.69 gm for women is in fact an estimate of the geometric mean. Also, the radiation dose effect is represented by the percentage change per Gy. For example, the estimated average (geometric mean) thyroid mass level for women decreased from 7.69 gm at 0 Gy to $7.69 \times 0.999^2 = 7.67$ gm at 2 Gy (2000 mGy). There was no significant trend of thyroid mass in relation to estimated radiation dose (two-tailed $p = 0.98$).

Table IX.Q-19. Parameter Estimates for Dose-Response Models: Thyroid Mass

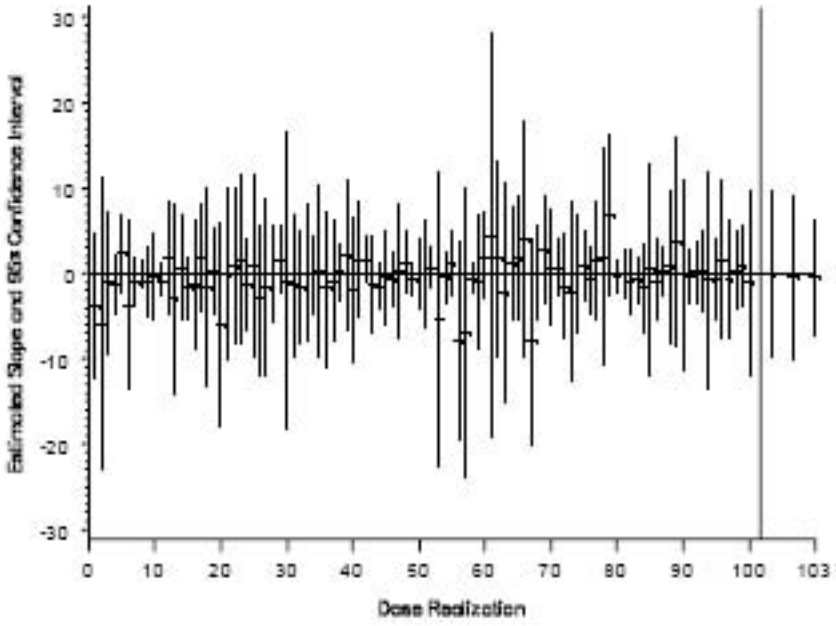
Parameter	Thyroid Mass (gm)
No. of living evaluable participants	3153
Estimated average background thyroid mass for women	7.69 (7.43, 7.96)
Estimated average background thyroid mass for men	11.51 (11.11, 11.92)
Estimated percentage change in average thyroid mass per Gy	–0.1% (–9.3%, +10.0%)
Statistical significance of dose-response (two-tailed p-value)	0.98

Entries for model parameters (background means and slope) in the tableare estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

Q.8.a. Uncertainty

The estimated slopes of the sex-stratified linear dose-response model for log of thyroid mass are shown in Figure IX.Q-22 for each of the 100 dose realizations produced by the CIDER model. The confidence intervals in that figure were calculated at the 98.33% confidence level, i.e., were adjusted by the Bonferroni technique for the simultaneous estimation of the slope and two sex-specific background rates. While the point estimate of the slope was greater than 0 for 45 of the 100 realizations, the confidence interval included 0 for all of the 100 realizations. Also shown in Figure IX.Q-22 (to the right of realization 100) are the estimates and confidence intervals calculated using (from left to right) the median, geometric mean, and mean of each participant's 100 dose realizations.

Figure IX.Q-22. Estimated Dose-Response for Thyroid Mass, by Dose Realization



R. Summary of Dose-Response Results

The primary evaluation of dose-response relationships focused on twelve categories of thyroid disease, hyperparathyroidism, and ultrasound-detected thyroid abnormalities of the thyroid. For each of these 14 outcome categories a primary case definition was specified based on the most definitive and valid diagnostic criteria available. The principal dose-response analysis used this primary definition of outcome, individual radiation dose estimates (the median for each individual) based on individual residence history, and on dietary consumption data from the CATI when available or on HEDR default values when CATI data were not available. The results from these analyses using the primary outcome definition constitute the principal findings of the HTDS. These results are summarized in Table IX.R-1 which shows that there are no significant dose-responses for the outcomes considered.

Table IX.R-1. Summary of Dose-Response Results for Thyroid Disease Outcomes

Thyroid Disease	Estimated Background Rates Female	Estimated Background Rates Male	Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
Thyroid Cancer	.006 ± .002 (.001, .011)	.002 ± .001 (0*, .005)	.002 ± .004 (< –.001, .017)	0.25
Benign thyroid nodule	.100 ± .008 (.081, .119)	.049 ± .006 (.034, .064)	–.008 ± .015 (< –.022, .041)	0.68
Total thyroid neoplasia	.011 ± .003 (.004, .018)	.006 ± .002 (.001, .012)	.001 ± .006 (< –.003, .022)	0.42
Any thyroid nodule	.112 ± .008 (.092, .132)	.053 ± .006 (.038, .068)	–.007 ± .016 (< –.023, .043)	0.65
Hypothyroidism	.118 ± .009 (.097, .139)	.037 ± .006 (.023, .050)	–.006 ± .019 (< –.016, .047)	0.61
Autoimmune thyroiditis	.239 ± .012 (.212, .267)	.133 ± .010 (.109, .156)	–.026 ± .026 (< –.057, .044)	0.82
Graves disease	.016 ± .004 (.008, .025)	.004 ± .002 (0*, .009)	–.001 ± .009 (< –.002, .024)	0.56
Autoimmune thyroid disease	.255 ± .012 (.227, .283)	.136 ± .010 (.112, .160)	–.024 ± .027 (< –.058, .048)	0.80
Hyperthyroidism	.077 ± .007 (.060, .094)	.015 ± .004 (.006, .025)	.011 ± .015 (< –.008, .052)	0.22
Multinodular thyroid gland	.040 ± .005 (.027, .053)	.014 ± .004 (.006, .023)	–.006 ± .016 (NE, .014)	0.88
Simple goiter	.006 ± .002 (.001, .011)	.003 ± .002 (0*, .008)	–.001 ± .008 (NE, .012)	0.74
Other thyroid disease	.010 ± .003 (.003, .016)	.003 ± .002 (0*, .008)	.002 ± .007 (< –.002, .024)	0.39

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, ">" indicates that the upper confidence limit is greater than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). "0*" indicates that the lower confidence limit for a background rate was less than 0.

Table IX.R-1. Summary of Dose-Response Results for Thyroid Disease Outcomes (continued)

Thyroid Disease	Estimated Background Rates Female	Estimated Background Rates Male	Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (one-tailed p-value)
Hyperparathyroidism	.006 ± .003 (0*, .013)	.001 ± .002 (0*, .006)	−.000 ± .018 (NE, .013)	0.61
Any UDA	.552 ± .014 (.519, .586)	.365 ± .014 (.332, .399)	.031 ± .038 (−.059, .116)	0.21
Palpable UDA	.090 ± .008 (.070, .110)	.043 ± .006 (.029, .057)	−.018 ± .023 (NE, .015)	0.95
Nonpalpable focal UDA	.451 ± .014 (.417, .484)	.303 ± .013 (.270, .335)	.027 ± .037 (−.061, .115)	0.23
Diffuse UDA	.174 ± .011 (.148, .199)	.084 ± .009 (.064, .105)	.029 ± .028 (−.029, .100)	0.14

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses ("<" indicates that the lower confidence limit is less than the indicated value, "NE" indicates the confidence limit was not estimated due to its close proximity to the point estimate). "0*" indicates that the lower confidence limit for a background rate was less than 0.

Less definitive criteria to identify cases were also defined for each outcome category using less definitive diagnostic criteria. Dose-response analyses were also conducted for each of these alternative definitions. In addition, dose-response analyses were conducted for six outcome categories based on the results of laboratory assays, and for thyroid mass estimated from the ultrasound scan (Table IX.R-2). The primary analysis for each outcome used the method of maximum likelihood to estimate the background rates or averages for women and men, and the slope of the sex-stratified linear models. Estimates of the parameters were also calculated using the method of least squares, once with doses treated as a continuous quantitative variable ("ungrouped analysis"), and again with doses treated as a categorical variable ("grouped analysis"). Linear quadratic and logistic dose-response models were also considered as alternatives to the linear model. Dose-response analyses for all outcomes were repeated using two alternative sets of individual dose estimates, and two alternative representations of exposure that did not use the HEDR models to estimate individual radiation dose. Efforts were also made to evaluate the influence of uncertainties in individual dose estimates on the fitted dose-response relationships for the primary case definition in each outcome category.

Table IX.R-2. Summary of Dose-Response Results for Laboratory Values and Thyroid Mass

Outcome	Estimated Background Rates Female	Estimated Background Rates Male	Estimated Slope of Dose-Response (per Gy)	Statistical Significance of Dose-Response (two-tailed p-value)
TSH by RIA (μIU/ml)	.90 ± .04 (.80, 1.00)	.89 ± .04 (.79, .99)	.02 ± .16 (–.36, .40)	0.90
TSH by EIA-1 (μIU/ml)	.46 ± .03 (.37, .54)	.31 ± .03 (.23, .39)	.13 ± .11 (–.13, .39)	0.22
TSH by EIA-2 (μIU/ml)	.39 ± .02 (.33, .45)	.23 ± .03 (.17, .29)	.01 ± .06 (–.13, .16)	0.82
T4 (μg/dl)	2.02 ± .01 (2.00, 2.03)	1.88 ± .01 (1.87, 1.90)	–.004 ± .02 (–.05, .04)	0.84
T3RU (μg/dl)	.021 ± .005 (.009, .032)	–.160 ± .005 (-.170, -.149)	–.01 ± .01 (–.04, .02)	0.36
FTI	1.998 ± .005 (1.99, 2.01)	2.044 ± .005 (2.03, 2.05)	.02 ± .01 (–.02, .05)	0.23
Anti-TPO (IU/ml)	–3.64 ± .42 (–4.65, 2.64)	–6.65 ± .54 (–7.95, -5.35)	–.39 ± .88 (–2.48, 1.71)	0.66
AMA (U/ml)	0.26 ± .30 (–.46, .99)	–1.24 ± .36 (–2.11, -.36)	–.51 ± .80 (–2.43, 1.42)	0.52
Anti-TG (IU/ml)	–4.01 ± .23 (–4.57, –3.45)	–5.71 ± .29 (–6.42, -5.01)	–.64 ± .50 (–1.84, 0.56)	0.20
Serum calcium (mg/dl)	9.2 ± .01 (9.14, 9.20)	9.2 ± .01 (9.16, 9.22)	–.09 ± .03 (–.16, –.01)	0.0074
Thyroid mass (gm)	2.04 ± .01 (2.00, 2.07)	2.44 ± .01 (2.41, 2.48)	–.00 ± .04 (–.10, .10)	0.98

Entries in the table are estimate ± standard error, with Bonferroni-adjusted 95% confidence interval in parentheses.

In overall summary of the dose-response results, there was no evidence of a statistically significant association between estimated thyroid radiation dose from Hanford and the cumulative incidence of any of the 14 primary thyroid or parathyroid disease outcomes or the prevalence of thyroid UDAs. There was also no evidence of any statistically significant dose-response relationship for any of the alternative definitions of outcome. The findings were essentially unchanged for analyses based on either of the two alternative sets of individual dose estimates. The results remained the same after taking into account (adjusting for the effects of) several factors that could potentially confound the relationship between radiation dose and the outcome of interest. There was no evidence of any statistically significant dose-response for any outcome that might be different from the linear model used in the primary analyses (e.g., a linear quadratic relationship). Incorporation of uncertainty in the dose estimates did not materially change the primary results for any of the outcomes.

The study also found no statistically significant associations between estimated thyroid dose from Hanford's ^{131}I and the average values of tests for thyroid function (TSH, T4, T3RU, FTI), of tests for anti-thyroid immune response (anti-TPO, AMA, anti-TG), or of thyroid mass. Only serum calcium, which was measured as a screening test for hyperparathyroidism, was found to vary significantly in relation to estimated thyroid dose from Hanford's ^{131}I: average calcium levels decreased significantly with increasing estimated thyroid radiation dose. However the decrease was small enough that calcium levels remained within the normal range, and less than 1% of the study participants were hypocalcemic.

Presented below are more detailed summaries of the results for each of the primary outcomes investigated.

Thyroid Cancer

Twenty (0.6%) of the 3440 living evaluable participants were diagnosed with thyroid cancer; 13 women (0.7%) and 7 men (0.4%). In all but one case, the diagnosis was based on histologic evidence from the HTDS examination (12) or prior histologic evidence (7).

Using the primary definition (19 total cases; 14 in-area) and maximum likelihood analysis of the sex-stratified linear probability model, the risk of thyroid cancer did not increase significantly with estimated dose ($p = 0.25$), with an estimated slope of 0.002 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.001 to 0.017 per Gy. Results obtained by least squares analysis using ungrouped or grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of thyroid cancer increased significantly with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Incorporation of uncertainty in the dose estimates did not materially change the primary results.

Benign Thyroid Nodule

Two hundred and forty-nine (7.2%) of the 3440 living evaluable participants had a diagnosis of benign thyroid nodule based on histologic or cytologic evidence arising from the HTDS examination or from a prior diagnosis; 170 (9.7%) women and 79 (4.7%) men. An additional 38 (1.1%) participants had diagnoses classified as clinical, and another 10 (0.3%) had diagnoses based solely on a report by the participant or his/her CATI respondent.

Using the primary definition (249 total cases; 235 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of benign thyroid nodule did not increase significantly with estimated dose ($p = 0.68$), with an estimated slope of -0.008 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.022 to 0.041 per Gy. Results obtained by least squares analysis using ungrouped or grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of benign thyroid nodule increased with increasing dose. Analyses which

considered less definitive criteria to identify cases, as well as other disease outcomes related to benign nodules (e.g., benign nodules and nodules suspicious for follicular neoplasm, benign nodule excluding non-neoplastic disease, solitary nodule detected without ultrasound, benign nodule excluding colloid-only nodules, and benign colloid nodules), and analyses which considered alternative dose estimates or representations of exposure, revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Total Thyroid Neoplasia

This outcome was defined to include participants with thyroid cancer based on HTDS or prior histology or benign thyroid nodule with a histologic type of follicular adenoma, based on HTDS or prior histology. A total of 33 (1.0%) of the 3440 living evaluable participants were included in this category; 20 (1.1%) women and 13 (0.8%) men.

Using the primary definition (33 total cases; 28 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of total thyroid neoplasia did not increase significantly with estimated dose ($p = 0.42$), with an estimated slope of 0.001 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.003 to 0.022 per Gy. Results obtained by least squares analysis using ungrouped or grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of total thyroid neoplasia increased with increasing dose. Analyses using alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Any Thyroid Nodule

This outcome was defined by the diagnosis of one or more of the following: benign thyroid nodule, thyroid cancer, or nodule suspicious for follicular neoplasm. A total of 281 (8.2%) of the 3440 living evaluable participants had this outcome based on histologic or cytologic evidence arising from the HTDS examination or from a prior diagnosis: 193 (11.0%) women and 88 (5.2%) men. Another 39 (1.1%) were based on clinical diagnoses by the HTDS or prior (palpable nodule with no available cytology or histology), and there were 10 living evaluable participants with a diagnosis of any thyroid nodule based solely on reports from the participant or his/her CATI respondent.

Using the primary definition (281 total cases; 261 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of any thyroid nodule did not increase significantly with estimated dose ($p = 0.65$), with an estimated slope of –0.007 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.023 to 0.043 per Gy. Results obtained by least squares analysis using ungrouped or grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of any thyroid nodule increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Hypothyroidism

Two hundred and sixty-seven (7.8%) of the 3440 living evaluable participants had a diagnosis of hypothyroidism based on the HTDS evaluation or on medical records with supporting documentation; 204 (11.7%) women and 63 (3.7%) men. An additional 105 (3.1%) living evaluable participants had a diagnosis of hypothyroidism based on medical records but without supporting documentation, and 30

(0.9%) were inferred from past or current thyroxine therapy. There were 193 (5.6%) cases based solely on reports of hypothyroidism from the participant or his/her CATI respondent.

Using the primary definition (267 total cases; 246 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of hypothyroidism did not increase significantly with estimated dose ($p = 0.61$), with an estimated slope of −0.006 per Gy, and Bonferroni-adjusted 95% CI ranging from less than −0.016 to 0.047 per Gy. Similar results were obtained using the least squares analyses of grouped or ungrouped data. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of hypothyroidism increased with increasing dose. Analyses which considered less definitive criteria to identify cases, as well as permanent hypothyroidism, and analyses which considered alternative dose estimates or representations of exposure, revealed no evidence of a dose-response relationship, although the estimated regression coefficients from logistic regression analyses using less definitive criteria to identify cases were somewhat larger. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Autoimmune (Hashimoto's) Thyroiditis

A total of 625 (18.2%) of the 3440 living evaluable participants had a diagnosis of autoimmune thyroiditis based on the HTDS evaluation or medical records with supporting documentation; 403 (23.1%) women and 222 (13.1%) men. Another three cases were based on medical records without supporting documentation, and one case was based solely on a report by the participant or his/her CATI respondent.

Using the primary definition (625 total cases; 582 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of autoimmune thyroiditis did not increase significantly with estimated dose ($p = 0.82$), with an estimated slope of −0.026 per Gy, and Bonferroni-adjusted 95% CI ranging from less than −0.057 to 0.044 per Gy. Similar results were obtained when the least squares model was fit using ungrouped or grouped data. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of autoimmune thyroiditis increased with increasing dose. Analyses which considered less definitive criteria to identify cases, additional outcomes related to the assay for antithyroid immune response, and autoimmune thyroiditis in combination with non-iatrogenic, permanent hypothyroidism, as well as analyses which considered alternative dose estimates or representations of exposure, revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Graves Disease

A total of 34 (1.0%) of the 3440 living evaluable participants had a diagnosis of Graves Disease based on the HTDS evaluation or on medical records with supporting documentation; 28 (1.6%) women and 6 (0.4%) men. Three (0.1%) living evaluable participants had a diagnosis of Graves Disease based on medical records without supporting documentation, and an additional thirteen (0.4%) were based solely on a report from the participant or his/her CATI respondent.

Using the primary definition (34 total cases; 32 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of Graves Disease did not increase significantly with estimated dose ($p = 0.56$), with an estimated slope of −0.001 per Gy, and Bonferroni-adjusted 95% CI ranging from less than −0.002 to 0.024 per Gy. Results obtained by least squares analysis using ungrouped or grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of Graves Disease increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or

effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Autoimmune Thyroid Disease

Autoimmune thyroid disease was defined by a diagnosis of autoimmune (Hashimoto's) thyroiditis or Graves disease based on the HTDS evaluation or medical records with supporting documentation. A total of 659 (19.2%) of the 3440 living evaluable participants were included in this category; 431 (24.7%) women and 228 (13.5%) men. These included 625 with autoimmune (Hashimoto's) thyroiditis and 34 others with diagnoses of Graves disease. An additional 4 (0.1%) living evaluable participants had a diagnosis of autoimmune thyroid disease based on medical records without supporting documentation (three with autoimmune thyroiditis, one with Graves disease). Eleven others (0.3%) were based solely on a report by the participant or his/her CATI respondent (one with autoimmune thyroiditis, 10 with Graves disease).

Using the primary definition (659 total cases; 614 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of autoimmune thyroid disease did not increase significantly with estimated dose ($p = 0.80$), with an estimated slope of –0.024 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.058 to 0.048 per Gy. Similar results were obtained when the least squares model was fit using ungrouped or grouped data. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of autoimmune thyroid disease increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Hyperthyroidism

A total of 161 (4.7%) of the 3440 living evaluable participants were diagnosed with hyperthyroidism based on the HTDS evaluation or medical records with supporting documentation; 134 (7.7%) women and 27 (1.6%) men. An additional 14 (0.4%) living evaluable participants had a diagnosis of hyperthyroidism based on medical records without supporting documentation, and 21 (0.6%) were based solely on a report from the participant or his/her CATI respondent. It is important to note that these 196 cases included a substantial number of iatrogenic cases (caused by excess thyroid hormone replacement). Since endogenous hyperthyroidism was of particular importance, analyses that focused on cases of non-iatrogenic hyperthyroidism were emphasized in this study.

Using the primary definition (161 total cases; 155 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of hyperthyroidism did not increase significantly with estimated dose ($p = 0.22$), with an estimated slope of 0.011 per Gy, and Bonferroni-adjusted 95% CI ranging from less than –0.008 to 0.052 per Gy. Similar results were obtained when the least squares model was fit using ungrouped or grouped data. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of hyperthyroidism increased with increasing dose. Analyses which considered less definitive criteria to identify cases, as well as non-iatrogenic hyperthyroidism, and analyses which considered alternative dose estimates or representations of exposure, revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Multinodular Thyroid Gland

A total of 95 (2.8%) of the 3440 living evaluable participants had a diagnosis of multinodular thyroid gland based on the HTDS evaluation; 73 (4.2 %) women and 22 (1.3 %) men. An additional

nineteen (0.6%) living evaluable participants had a diagnosis of multinodular thyroid gland based on medical records, and one diagnosis was based solely on a report from the participant or his/her CATI respondent.

Using the primary definition (95 total cases; 85 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of multinodular thyroid gland did not increase significantly with estimated dose ($p = 0.88$), with an estimated slope of -0.006 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.014 per Gy. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was even more negative than the maximum likelihood estimate, thereby providing no evidence that risk of multinodular gland increased with increasing dose ($p = 0.89$ and 0.83, respectively). There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of multinodular thyroid gland increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Simple Goiter

The diagnosis of simple goiter was uncommon, with only 14 (0.4%) of the 3440 living evaluable participants having this diagnosis based on HTDS evaluation; 9 (0.5%) women and 5 (0.3%) men. Another 28 (0.8%) had diagnoses based on medical records, and for an additional 28 (0.8%) the diagnosis was based solely on a report by the participant or his/her CATI respondent.

Using the primary definition (14 total cases; all in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of simple goiter did not increase significantly with estimated dose ($p = 0.74$), with an estimated slope of -0.001 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.012 per Gy. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was even more negative than the maximum likelihood estimate, thereby providing no evidence that risk of simple goiter increased with increasing dose ($p = 0.79$ and 0.70, respectively). There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of simple goiter increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Other Thyroid Disease

Four living evaluable participants, all in the in-area group, had diagnoses of other thyroid disease based on their HTDS examinations or medical records with supporting documentation. These included two cases of subacute thyroiditis in women; one case of familial thyroglobulin binding deficiency in a male; and one case of secondary hypothyroidism in a female. The first alternative definition added only two cases with diagnoses based on medical records without supporting documentation. Both were cases of subacute thyroiditis in women. For both the primary and first alternative definition of other thyroid disease, there were too few cases for meaningful estimation of the radiation dose-response.

The second alternative definition added 20 participants, primarily with participant or CATI respondent reports of past thyroid disease of unknown type. This brought the total number of cases to 26, of whom four were out-of-area participants. Based on maximum likelihood analysis of the sex-stratified linear probability model using this case definition, the estimated slope was slightly greater than zero (0.002 per Gy) with Bonferroni-adjusted 95% CI ranging from less than –0.002 to 0.024 per Gy, providing no evidence that cumulative incidence increased significantly with increasing dose (one-tailed $p = 0.39$).

Because the number of cases in this category was small, and the diagnoses were heterogeneous and mostly unknown, further analyses of this outcome were not performed.

Hyperparathyroidism

A total of 12 (0.3%) living evaluable participants had a diagnosis of hyperparathyroidism based on the HTDS evaluation or on medical records with supporting documentation; 10 (0.6 %) women and 2 (0.1%) men. Another two diagnoses were based on a report from the participant or his/her CATI respondent. One additional living evaluable participant who did not meet the study's criteria for hyperparathyroidism nevertheless had an elevated calcium in the presence of a high normal PTH level, when the PTH should have been suppressed, highly suggestive of hyperparathyroidism. This participant was included as a case in an additional analysis.

Using the primary definition (12 total cases; 11 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of hyperparathyroidism did not increase significantly with estimated dose ($p = 0.61$), with an estimated slope of –0.0001 per Gy. The lower limit of the Bonferroni-adjusted 95% confidence interval was not estimated, but the upper limit was 0.013 per Gy. When the model was fit by the method of least squares, the estimated slope using either ungrouped or grouped data was slightly more negative than the maximum likelihood estimate, thereby providing no evidence that risk of hyperparathyroidism increased with increasing dose ($p = 0.74$ and 0.75, respectively). There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of any thyroid nodule increased with increasing dose. Analyses which considered less definitive criteria to identify cases and alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

The thyroid gland was visible in the ultrasound examinations of 3429 of the 3440 living evaluable participants. For 11 participants the thyroid was not visible, 10 because of thyroid surgery and one because the sonographer couldn't adequately visualize the thyroid. Among the 3429 whose thyroids were visible, 1596 (46.5%) had one or more ultrasound-detected thyroid abnormalities (thyroid UDAs); 964 (55.5 %) women and 632 (37.4 %) men. Ultrasound findings were categorized as palpable thyroid UDAs (224 or 6.5%), nonpalpable focal thyroid UDAs (1309 or 38.2%), and diffuse thyroid UDAs (458 or 13.4%). All three types of UDA were more frequent among women than men. Ultrasound-detected thyroid abnormalities were based only on the HTDS evaluation, not on any prior ultrasounds.

For any UDA (1596 total cases; 1481 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of any UDA did not increase significantly with estimated dose ($p = 0.21$), with an estimated slope of 0.031 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.059 to 0.116 per Gy. Estimation by least squares using the ungrouped data gave nearly identical results, and the least squares fit to the grouped data were similar. There was no evidence from the linear-quadratic or logistic regression model that the cumulative incidence of any UDA increased with increasing dose. Analyses which considered alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

For palpable UDAs (224 total cases; 204 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of a palpable UDA did not increase significantly with estimated dose ($p = 0.95$), with an estimated slope of -0.018 per Gy. The Bonferroni-adjusted lower 95% confidence limit was not estimated due to the magnitude of the negative slope estimate, however the upper confidence limit was 0.015 per Gy. Estimation by least squares using either the ungrouped or grouped data gave nearly identical results. There was no evidence from the linear-quadratic or logistic regression model that the prevalence of palpable thyroid UDAs increased with increasing dose. Analyses which considered

alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

For nonpalpable focal UDA (1309 total cases; 1217 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of a nonpalpable focal UDA did not increase significantly with estimated dose ($p = 0.23$), with an estimated slope of 0.027 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.061 to 0.115 per Gy. Estimation by least squares using either the ungrouped or grouped data gave nearly identical results. There was no evidence from the linear-quadratic or logistic regression model that the prevalence of nonpalpable focal thyroid UDAs increased with increasing dose. Analyses which considered alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

To assess whether the dose-response results might be affected by the size of focal thyroid UDAs, three additional outcomes were analyzed. These included the presence of a focal UDA with maximum dimension at least 5 mm, the presence of a focal UDA with maximum dimension at least 10 mm, and the presence of a focal UDA with average dimension at least 15 mm. These additional analyses applied only to palpable and nonpalpable focal thyroid UDAs, since diffuse UDAs were not defined by any size criterion. In none of these additional analyses was there any evidence that the risk of having a focal UDA of a particular size increased with increasing dose ($p=0.64$, 0.88 and 0.53 for the presence of focal UDA with maximum dimension of 5 mm, maximum dimension of 10 mm and average dimension of 15 mm, respectively).

Additional analyses were performed to investigate whether the number of thyroid UDAs detected in individual participants might increase in relation to estimated thyroid radiation dose. For each living evaluable participant with an HTDS ultrasound examination, the numbers of focal thyroid UDAs with maximum dimension ≥ 5 mm, maximum dimension ≥ 10 mm, and average dimension ≥ 15 mm were counted. Study participants had as many as nine thyroid UDAs with maximum dimension ≥ 5 mm, although the majority (60% of the women and 74% of the men) had no such thyroid UDAs. The overall average number of thyroid UDAs of this size was 0.84 per person for women, and 0.47 per person for men. Results of fitting sex-stratified Poisson regression models for the relationship between estimated thyroid radiation dose and number of focal thyroid UDAs indicated that the average number of such thyroid UDAs per person did not increase significantly with estimated dose ($p = 0.80$, 0.48 and 0.43 for the number of thyroid UDAs with maximum dimension of 5mm, maximum dimension of 10 mm and average dimension of 15 mm, respectively.). The Bonferroni-adjusted 95% confidence interval for the dose-response parameter for number of thyroid UDAs with maximum dimension of 5 mm ranged from 0.72 to 1.17, encompassing a range from 28% decrease to 17% increase per Gy. The results for the number of thyroid UDAs with maximum dimension of 10 mm and average dimension of 15 mm were similar.

Using the primary definition of diffuse UDA (458 total cases; 428 in-area), and maximum likelihood analysis of the sex-stratified linear probability model, the risk of a diffuse UDA did not increase significantly with estimated dose ($p = 0.14$), with an estimated slope of 0.029 per Gy, and Bonferroni-adjusted 95% CI ranging from –0.029 to 0.100 per Gy. Estimation by least squares using either the ungrouped or grouped data gave nearly identical results. There was no evidence from the linear-quadratic or logistic regression model that the prevalence of diffuse thyroid UDAs increased with increasing dose. Analyses which considered alternative dose estimates or representations of exposure revealed no evidence of a dose-response relationship. Accounting for potential confounding or effect modification, and incorporation of uncertainty in the dose estimates, did not materially change the primary results.

Laboratory Tests

Of the 3191 living evaluable in-area participants, 3183 (99.7%) consented to provide a blood specimen at their HTDS clinic. Several laboratory assays were conducted to evaluate thyroid function, anti-thyroid antibody response, and serum calcium level. In addition to the dose-response analyses conducted of specific thyroid disease outcomes which incorporated information from these tests in the determination of the diagnosis, dose-response analyses were also conducted to investigate whether there were associations between the laboratory values from these tests and estimated thyroid radiation dose from Hanford (i.e., regardless of thyroid disease diagnosis).

Thyroid stimulating hormone (TSH) levels were determined according to three different tests over the course of the study. Of the 3183 living evaluable in-area participants who provided blood samples, 222 were receiving exogenous thyroid hormone at the time of their HTDS clinic. These 222 were excluded from the analyses of TSH. Among the remaining 2961 living evaluable participants, 584 had TSH measured by RIA, 810 by EIA-1, and 1567 by EIA-2. There was no evidence of a significant trend in relation to estimated radiation dose for any of the three assays considered individually ($p = 0.90$, 0.22, and 0.82 for RIA, EIA-1, and EIA-2, respectively). When a generalization of the sex-stratified model was examined using all 2961 living evaluable participants with TSH measurements, in which the mean values of log(TSH) were assumed to differ between the sexes and to differ according to the type of assay, there was still no significant trend of average log(TSH) in relation to estimated thyroid radiation dose ($p = 0.42$).

Analyses of total thyroxine (T4) and triiodothyronine resin uptake (T3RU) were also conducted excluding the 222 living evaluable in-area participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic. Additionally, the T4 and T3RU values were unknown for two in-area participants due to insufficient volumes of collected blood. There was no significant trend of either T4 or T3RU in relation to estimated radiation dose ($p = 0.84$ and 0.36, respectively).

Free thyroxine index (FTI) was analyzed excluding the 222 living evaluable in-area participants who were receiving exogenous thyroid hormone at the time of their HTDS clinic. The FTI values were unknown for six additional in-area participants: the two with unknown T4 and T3RU, and four others for whom either T4 or T3RU was below its level of detection. There was no significant trend of FTI in relation to estimated radiation dose ($p = 0.23$).

Anti-TPO or AMA values were used for the anti-thyroid autoimmune response evaluations of 1562 and 1620 in-area living evaluable participants, respectively. Neither assay result was available for eight participants who declined to provide a blood sample, and for one other whose sample was of insufficient volume. There was no significant trend of either assay result in relation to estimated radiation dose ($p = 0.66$ for anti-TPO, 0.52 for AMA). Anti-thyroglobulin antibody (anti-TG) values were available for 3170 of the in-area living evaluable participants. There was no significant trend of anti-TG in relation to estimated radiation dose (two-tailed $p = 0.20$).

Serum calcium levels were measured in an effort to identify study participants with hypercalcemia which might be secondary to hyperparathyroidism. Of the 3183 living evaluable in-area participants who provided blood samples, 227 with diagnoses of hypothyroidism or hyperthyroidism based on the HTDS examination were excluded from the primary analysis of serum calcium levels. Two additional participants did not have serum calcium data due to insufficient volumes of collected blood. There was a statistically significant trend of decreasing serum calcium level in relation to increasing radiation dose ($p = 0.0074$), with an estimated slope of -0.09 per Gy and Bonferroni-adjusted 95% CI ranging from -0.16 to -0.01. Although there is no readily apparent explanation for this result, this finding deserves further comment. First, it should be noted that the laboratory test used measured the total serum calcium and not ionized calcium, which is the true measure of normal calcium levels in the blood. Thus, it cannot be certain that a dose effect would be present if ionized calcium rather than total calcium had been measured. Second, the outcome for which calcium was being measured, hyperparathyroidism, was not found to be associated with radiation dose. Third, the dose effect occurred primarily in the normal calcium range. For both women and men, the estimated background means were about $9.2 \pm .01$, consistent with the normal range of the test

(8.4-10.2). Only 0.9% of the cohort had low calcium levels less than 8.4 mg/dl (hypocalcemia). There was no statistically significant relationship between hypocalcemia and radiation dose. Even at a dose of 3 Gy (3000 mGy), which is larger than the maximum estimated dose of any study participant, average calcium levels predicted by the regression model were will within the normal range. Therefore, despite the *statistically* significant decrease in calcium levels with increasing dose, the resulting effect or clinical impact does not appear to be *clinically* significant.

Estimates of thyroid mass were available for 3400 living evaluable participants for whom both lobes of the thyroid were visible on ultrasound; 3153 were in-area participants. There was no significant trend of thyroid mass in relation to estimated radiation dose ($p = 0.98$).

X. DISCUSSION

A. Summary of Study Design and Execution

The purpose of the Hanford Thyroid Disease Study was to determine whether thyroid morbidity is increased among people exposed to atmospheric releases of ^{131}I from the Hanford Nuclear Site between 1944 and 1957. The primary objective of the research was to describe in what way any increase in thyroid disease observed is related to the dose of radiation received (that is, to describe the characteristics of any dose-response relationship). Additional objectives of the project were to: 1) determine whether hyperparathyroidism is increased among people exposed to the Hanford radiation releases; 2) assess the methods used to carry out such a study, and the degree to which such an investigation can be successfully planned and executed; and 3) provide information to residents of the surrounding communities regarding the conduct of the study and the findings and results.

In order to achieve the primary objective stated above, the study was conducted as a retrospective follow-up (cohort) study. As described more fully in section IV.A above, this design entailed the selection of a relatively large cohort of people who would have been exposed to Hanford radiation as young children, and who would represent the full range of possible doses to the thyroid from Hanford. The overall goal of the study was to locate all individuals in the cohort, obtain their consent to participate in the project, collect detailed information regarding their early childhood in order to estimate the dose of radiation they received to the thyroid from Hanford, and determine whether they have developed any form of thyroid disease or hyperparathyroidism since their exposure. The primary determination of whether there has been an increase in thyroid disease as a result of radiation exposure from Hanford was made by assessing the cumulative incidence of thyroid disease in relation to the level of individual thyroid radiation dose (i.e., the radiation dose-response), within members of the cohort.

This approach of using one population comprised of individuals with different levels of exposure to radiation has been used extensively in assessing the effects of radiation exposure in human populations. It is a common design in epidemiology, and has been of particular value in studies of atomic bomb survivors in Japan, in numerous studies of people exposed to radiation through medical procedures, and in the study of people exposed to radiation from atmospheric testing in Utah. This method is superior to the alternative approach of attempting to compare thyroid disease occurrence in a cohort under extensive study such as the HTDS cohort with that in a separate population presumed to be unexposed to radiation. This is because thyroid disease rates may be a function of a number of factors other than exposure to radiation, which may differ considerably between different populations. This is particularly true if one population is under careful study and diagnostic evaluation. Such differences can include: 1) the methods of diagnosis employed; 2) the extent to which diagnostic tests are implemented in a population (i.e., the thoroughness of the diagnostic process); 3) the dietary practices of the population; 4) the level of iodine in the diet; and 5) the composition of the population according to age, gender, and ethnicity. To the extent differences in such factors exist, it would be impossible to attribute any differences in thyroid disease rates observed to Hanford radiation exposure, as opposed to one or more of these other factors. The approach used in the HTDS is also superior to one which would implement the full HTDS protocol in a population geographically removed from the Hanford site, in an attempt to include people with no exposure from Hanford radiation. Although the methods and thoroughness of the diagnostic evaluation would be comparable under such circumstances, it would still not be possible to ensure comparability between the two study populations regarding the other types of possible differences listed above that could influence thyroid disease occurrence. Thus, to ensure as much comparability as possible regarding factors other than radiation that can influence the occurrence of thyroid disease, all comparisons of thyroid disease rates in relation to thyroid radiation dose level were made within the defined cohort.

The study cohort was defined based on place and year of birth in a manner designed to identify people with a full range of possible thyroid doses from Hanford. This was difficult to do, as no information was available regarding exposure or estimated dose to specific individuals. Using preliminary information available at the time of the design of the HTDS from the HEDR Project regarding the timing of the

radiation releases, movement of radioactive materials through the environment, and uptake by humans, a sampling scheme was developed to select individuals born in one of seven counties in the region around Hanford between 1940 and 1946.

From the outset it was recognized that such a design would present substantial challenges. The study would require that: 1) people be traced and located over a period of more than 40 years, based only on information contained on their birth certificate; 2) a person knowledgeable of each participant's early childhood be located, and be willing and able to provide detailed information about the person's childhood residence history and dietary habits; 3) participants be willing to travel to the Northwest and undergo a thorough medical evaluation for thyroid disease, including an ultrasound scan, blood tests, and potentially a thyroid biopsy; and 4) participants be willing to provide consent for independent review of prior medical records and diagnostic evaluations. Since no study of this type had ever been attempted before, it was not clear that such an approach would prove feasible.

As described more fully in section V above, the field components of the study were highly successful. A roster of 12,706 births was constructed from Washington State birth certificates, and 5199 individuals were selected for inclusion in the cohort. Of these, 4350 individuals (84%) were located alive and their identity confirmed, and 527 (10%) were confirmed as deceased. Importantly, success in locating individuals did not vary appreciably by sex, geographic region at the time of birth, or year of birth. Of those known to be deceased or who died prior to participation (16), a death certificate was obtained for verification of cause of death for 504 (93%).

Once contacted, individuals were cooperative and interested in participating. Of 4239 people contacted by phone to request participation, 3564 (84%) agreed to participate. Only 634 (15%) refused. Forty-one living located cohort members (0.9%) were determined to be unable to fully participate and were consequently not included in the study regardless of willingness to participate. Agreement to participate did not vary appreciably according to sex, geographic region at the time of birth, year of birth, or location of current residence. Of the 3564 who agreed to participate, 2712 participants identified a possible CATI respondent. Interviews were completed for 2266 (84%). However, not all of those for whom a CATI was completed attended a clinic. Thus, of the 3440 living evaluable participants included in the analysis, 2123 (62%) had a CATI interview that was used as the basis for dose estimation. Quality assessment of the respondent's ability to answer the interview questions was also performed (see section V.D). Following each section of the interview, interviewers recorded their assessment of how reliable the responses were for questions within that section. Assessments were recorded as: 1) Very Reliable; 2) Somewhat Reliable, or 3) Unreliable. Overall, the interviewers rated the quality of the data obtained in the CATI as very reliable.

It proved feasible to hold all clinics in the Pacific Northwest (all but one site was located in Washington), and participants were willing to travel from throughout the United States and even from abroad to attend clinics. Of those who agreed to participate, and who did not withdraw from the study at a later time, 97% (3447 of 3564) attended a HTDS clinic. Success in scheduling people for clinics did not vary substantially by sex, geographic area of birth, year of birth, or even current residence. Of those attending a clinic, almost all (> 99 %) participated in all aspects of the evaluation: In-Person Interview, thyroid ultrasound, blood tests, and clinical examination. Of the 272 participants for whom a fine needle aspiration biopsy of the thyroid was recommended, 259 (95%) underwent the procedure.

It also proved feasible to locate and retrieve prior medical records and materials. Attempting to locate and obtain records from as long ago as fifty years was expected to be one of the most difficult aspects of the HTDS. A total of 694 participants identified prior medical records of potential interest, and provided consent to the HTDS to request 1259 separate medical records. Of these, 795 (63%) were received by the HTDS from 494 of the 694 participants (71%). Pathology or cytology slides were requested for 52 of the 694 individuals identifying historical material. Of these, slides were received from 42 (81%).

The results of the field components of the HTDS reflect a relatively uniform and high level of success in achieving the objectives set forth for each. It proved feasible to identify a large group of people exposed at varying levels to radiation releases from Hanford, to locate and contact them, to enroll them in the study, to collect information needed to estimate their individual radiation dose to the thyroid, to

examine them for the presence or history of thyroid disease, and to review prior medical records relevant to prior evaluations or diagnoses of thyroid disease. Given the eligibility criteria for inclusion in this study, there was no evidence that success in these various tasks varied appreciably according to a person's sex, where they were born, when they were born, or where they currently live. Because these operational results provide no indication of substantial differential success in aspects of the study related to subject selection, inclusion, and data collection that might potentially bias or influence dose-response relationships, they provide an important framework for interpreting the specific findings regarding radiation dose and the thyroid outcomes under study.

B. Summary of Dose-Response Results

The primary evaluation of dose-response relationships focused on twelve categories of thyroid disease, ultrasound-detected abnormalities of the thyroid, and hyperparathyroidism. For each of these 14 outcome categories a primary case definition was specified based on the most definitive and valid diagnostic criteria available. The diagnostic information used for each primary outcome definition was obtained at the time of the participant's clinical evaluation at an HTDS clinic site. This information included results from thyroid physical examinations, laboratory tests, ultrasound scans, and thyroid biopsy results. For most outcomes, if a participant's prior medical records confirmed a diagnosis with the same diagnostic methods as those used at the HTDS clinic evaluation, such information was classified as having met the criteria for the primary outcome definition. The principal dose-response analysis used this primary definition of outcome, individual radiation dose estimates (the median for each individual) based on individual residence history, dietary consumption data from the CATI or expanded In-Person Interview when available, and HEDR default values when such data were not available. The results from these analyses using the primary outcome definition constitute the principal findings of the HTDS. The primary analysis for each outcome used the method of maximum likelihood to estimate the background rates or averages for women and men, and the slope of the sex-stratified linear models. Estimates of the parameters were also calculated using the method of least squares, once with doses treated as a continuous quantitative variable ("ungrouped analysis"), and again with doses treated as a categorical variable ("grouped analysis"). Linear quadratic and logistic dose-response models were also considered as alternatives to the linear model.

Alternative case definitions were also specified for each outcome category using less definitive diagnostic criteria. The diagnostic information used for the alternative case definitions did not meet the HTDS primary outcome criteria, but was obtained from additional sources. These sources included statements from medical records for which the diagnosis could not be confirmed, or reports from the participant or his or her CATI respondent of a diagnosis for which no medical records could be found. Dose-response analyses were also conducted for each of these alternative definitions. In those instances where an alternative definition resulted in a substantially greater number of people in the analysis than the primary definition, the dose-response results for the alternative definition are also presented in the Results section. In addition, dose-response analyses were conducted for six outcome categories based on the results of laboratory assays, and for thyroid mass estimated from the ultrasound scan.

All dose-response analyses for all outcome definitions were repeated using two alternative sets of individual dose estimates: 1) individual residence history, and only HEDR default data regarding dietary consumption (i.e., no data from the CATI or expanded In-Person Interview); and 2)individual residence history, dietary consumption data from the CATI or expanded In-Person Interview when available, and default values based on the HTDS CATI data when such individual data were not available (with the exception of consumption other than milk for expanded IPIs for which HEDR defaults were used). Further, two alternative representations of exposure were defined which did not use the HEDR models to estimate individual radiation dose. Although these categorizations of exposure were more crude than the individual quantitative estimates of dose, such analyses were performed as an alternative means of investigating a possible relationship between the thyroid outcomes under study and exposure to Hanford radiation that would be independent of the HEDR models and assumptions.

Because the primary focus of the HTDS analysis was to investigate possible dose-response relationships, and because individual radiation doses estimated in this study were characterized by some degree of uncertainty due to the uncertain nature of many of the parameters that determine dose, efforts were also made to evaluate the influence of dose uncertainties on the fitted dose-response relationships for the primary case definition in each outcome category. Two different approaches were used. First, the linear dose-response models were fit using each of the 100 realizations of thyroid dose obtained from the HEDR models. The estimate of, and 95% confidence interval for, the slope of the dose-response from each of these 100 analyses were displayed graphically to illustrate how the estimated radiation effect varied among the 100 realizations of dose, and how these estimates compared to the results based on the median or other average dose estimate.

In the second approach, Bayesian analysis was used to estimate the parameters of the logistic dose-response model that were adjusted for the effect of the dose uncertainty. This approach used the Gibbs sampling technique to estimate the marginal posterior distribution of the model parameters, conditional on the observed data, from the joint conditional distribution of the parameters and unobserved true doses. For each primary outcome definition, the estimated marginal posterior distribution of the regression coefficient was displayed. Also the median and appropriate percentiles of that distribution were used to derive uncertainty-adjusted point and confidence interval estimates of the dose-response coefficient, for comparison to the corresponding unadjusted estimates. As expected, the effect of this adjustment for uncertainty was generally to increase the magnitude of the estimated dose-response coefficient. That is, if the unadjusted estimate was less than 0, then the adjusted estimate was even more negative. Similarly, if the unadjusted estimate was greater than zero, the adjusted estimate was even larger. Also as expected, however, the adjustment for uncertainty reduced the precision with which the regression coefficient was estimated, i.e., the uncertainty-adjusted confidence intervals were wider than the corresponding unadjusted intervals. Consequently for none of the outcomes did the adjustment for dose uncertainty reveal a significant dose-response that was obscured in the unadjusted analyses.

In overall summary of the dose-response results, there was no evidence of a statistically significant association between estimated thyroid radiation dose from Hanford and the cumulative incidence of any of the 14 primary outcomes. There was also no evidence of any statistically significant dose-response relationship for any of the alternative definitions of outcome. These results were remarkably uniform. The findings were essentially unchanged for analyses based on either of the two alternative sets of individual dose estimates. The results remained the same after taking into account (adjusting for the effects of) several factors that could potentially confound the relationship between radiation dose and the outcome of interest. There was no evidence of any statistically significant dose-response for any outcome that might be different from the linear model used in the primary analyses (e.g., a linear-quadratic relationship). Incorporation of uncertainty in the dose estimates did not materially change the primary results for any of the outcomes.

C. Consideration of Factors Related to Study Design and Execution

In interpreting the findings of an epidemiologic study like the HTDS, it is important to consider the possible influence on the results of factors other than those directly accounted for in the analysis. Of particular concern is the possibility that the results could be due in part (or entirely) to artifacts or flaws in either the design or conduct of the study. A number of different factors are considered below in an attempt to better understand the absence of any dose-response relationships found with any of the outcomes investigated in this study.

C.1. Factors Related to Cohort Definition and Selection

A fundamental consideration in interpreting these results is the adequacy and appropriateness of the study group upon which all analyses are based. Two principal aspects of this question must be addressed: 1) was the definition and selection of the study group adequate in order to achieve the primary research objective; and 2) were the analyses based on an unbiased representation of this group?

The primary research objective of this study was to determine whether thyroid disease is increased among people exposed to atmospheric releases of radioactive iodine from the Hanford Nuclear Site between 1944 and 1957. A study group was defined with the intention of identifying individuals who could have been exposed based on their proximity to the site during the times when the releases were highest. Further, to have the greatest likelihood of detecting an effect of exposure, the study group was restricted to include people who would have been young children at the time of greatest exposure. This was based on the assumption that young children receive a higher dose to the thyroid from ^{131}I for the same level of exposure than do adolescents or adults, and that the thyroid gland in young children may be more susceptible to the effects of a given dose than in older people.

A study group was therefore defined based on births that occurred in the region. A roster of births to mothers living in a seven-county area between 1940 and 1946 was constructed from Washington State birth records. The HTDS cohort was selected from this roster using a stratified random sampling technique. Thus, the study group of 5199 individuals selected for inclusion in the HTDS reflects a random sample of a complete listing of births, and as such provides a population of people who could have been exposed to the Hanford releases at young ages. It does not define the total population in the region who could have been exposed, nor even the total population of the age range encompassed by the selected birth cohort who could have been exposed. However, in order to achieve the objectives set forth using a cohort study design, it is not necessary to investigate the entire population at risk or even a representative sample thereof. In this instance, restricting the definition of the cohort in some manner (in this case as a birth cohort) is not of concern in terms of introducing a possible bias in the dose-response. The more important issue is whether the study group is defined in a manner that will include people representing the entire range of possible doses, that will include adequate numbers of people with the highest as well as the lowest doses, and that will allow for uniform and complete follow-up to ascertain thyroid disease status for everyone in the group in the same manner. Based on what is known about the Hanford radiation releases and possible exposures to people in the region, the definition and selection of the HTDS cohort should be quite adequate to achieve the primary research objectives.

A more critical consideration is the question of who actually ended up participating in the study and contributing to the analyses of dose-response. Ideally, the analysis would reflect a complete evaluation of all 5199 members of the defined cohort. However, loss of information occurs for several reasons, particularly in a study such as this one where the exposure occurred so long ago: inability to locate people, refusal to participate, inability to participate for other reasons, and mortality within the cohort. The primary concern with such losses is the possibility that people who are not included in the final analyses are somehow different in a systematic way that might be related to both: 1) radiation dose from Hanford; and 2) one of the thyroid outcomes under study. If so, failure to include such people could potentially result in a misleading or incorrect estimate of any dose-response relationship.

This study was successful in locating members of the cohort. As reported in section V.B.4., approximately 94% of the 5199 individuals originally identified were located: 4350 alive and 527 deceased. Furthermore, there was no evidence of an appreciable difference in ability to locate people according to sex, year of birth (and thus age at exposure), or geographic area of birth within the Hanford region. The proportion located in each of these subgroups was high (over 90%), and relatively uniform.

Once located and contacted approximately 84% of those contacted agreed to participate. This high level of cooperation was also relatively uniform among the various subgroups defined by sex, year of birth, and geographic area of birth. There was no evidence of any subgroup of the cohort being substantially more or less likely to agree to participate. This pattern also was apparent according to geographic area of current residence. There was no indication that people who live outside of the region were less likely to agree to participate. Across all areas of the country, the proportion agreeing to participate was uniformly around 80%.

Approximately 15% of those contacted refused participation, or withdrew from participation (even though they initially agreed to participate). An attempt was made to identify a reason for each refusal or withdrawal based on responses to the refusal questionnaire (if the person was willing to provide such information) and the recruiter's assessment of the interaction with the person. The majority of the refusals

and withdrawals were because the person was not interested, or did not have time. Very few refused because they were opposed to the study. Potentially of more interest is the group who refused or withdrew because of illness or impairment, which precluded them from participating. The principal concern would be that people in this group were more likely to have one of the outcomes under study. In only one case was current thyroid disease given as a reason for non-participation. Further, in reviewing the types of illnesses and impairments cited, there is no indication that people who refused or withdrew were more or less likely to have any of the disease outcomes investigated in the study. Although it is not possible to say with certainty from these data that people who chose not to participate are no different regarding the outcomes of interest than those who did participate, these responses provide some assurance that such is the case. In addition, given the relatively small proportion of people who refused or withdrew, and the uniformity of this proportion among subgroups of the cohort, it is unlikely that such losses could have materially biased the dose-response analyses.

Loss of information also occurs because of mortality within the cohort. Of potential concern is the possibility that such loss is related to one or more of the outcomes of interest. In this study, 527 (10.1%) of the 5199 individuals originally identified were confirmed as deceased and an additional 16 (0.3%) who were located alive died before participating in the HTDS. A death certificate was obtained for 504 (93% of the 543) in order to determine the cause of death for each person. There were 199 deaths in females and 344 deaths in males, with no known age of death for two of the males. For both sexes, the largest proportion of deaths occurred under one year of age (36% for both males and females). Most of these deaths were due to conditions in the perinatal period or congenital anomalies. Approximately 31% of the deaths in females were due to these two causes, as were approximately 27% of the deaths in males.

An analysis was conducted to investigate whether the mortality experience in this cohort overall was unusually high, relative to what would be expected based on the mortality experience of the regional population from the same time period, and to determine whether there was any indication of an excess in mortality from conditions that might be related to one or more of the primary thyroid outcomes of interest. The detailed results of this analysis are shown in Mortality Appendix 23. In summary, there was no overall increase in total mortality over what would be expected based on the mortality experience of the population of Washington State during the same time period (standardized mortality ratio (SMR) = 0.97; 95% Confidence Interval (CI) = 0.89, 1.06). This was true for both females (SMR = 0.96) and males (SMR = 0.98). However, there was an excess in deaths due to conditions of the perinatal period (SMR = 1.69, 95% CI = 1.39, 2.04), which was found in both females (SMR = 1.70) and males (SMR = 1.68).

Further analyses were performed to investigate whether there was any excess in mortality according to geostratum of birth, or in birth years concentrated around the time of the peak releases from Hanford (i.e., in the birth cohorts defined by the period 1945-46). The only excess in mortality observed by geostratum was among people born in Franklin County (SMR = 1.61, 95% CI = 1.15, 2.20). This excess was found for males (SMR = 1.66, 95% CI = 1.09, 2.44), but was only suggestive for females (SMR = 1.53, 95% CI = 0.83, 2.56). There was essentially no difference in mortality seen between the 1945-46 birth cohorts and the 1940-1944 birth cohorts. Analyses were also conducted according to year of death, classified as before 1945 (beginning of Hanford operations) and 1945 or later. For total mortality, there was little difference in the SMRs for deaths before 1945 and for the period from 1945 on (SMR = 1.06 vs. 0.95, respectively), and neither was statistically significant. This pattern was similar in males and females, and was observed for conditions of the perinatal period and for congenital anomalies.

Of primary interest in considering the results of these exploratory analyses regarding mortality in the HTDS cohort is whether the loss of cohort members through death could in some way bias the dose-response analyses. Given the principal findings of the study, the primary concern would be that this loss attenuated a true dose-response (i.e., biased the estimate of effect toward the null), and that is why no association is observed between increasing radiation dose from Hanford and the outcomes under study. In order for the exclusion of participants lost to death to mask a true dose-response, one of three circumstances would have to be operative among the group of 543 deceased individuals: 1) they would have had to have experienced disproportionately higher doses *and* higher rates of the outcomes under study, thereby "pulling up" the high end of the dose-response curve; 2) they would have had to have experienced disproportionately low doses *and* low rates of the outcomes under study, thereby "pulling

down" the low end of the dose-response curve; or 3) they would have had to have experienced the full range of possible doses, but exhibited a *very strong* dose-response over the full dose range. Given the relatively small proportion of the cohort lost due to deaths (10%) and the consistency of findings of an absence of a radiation dose-response across all outcomes, it is highly unlikely that the absence of a dose-response is due to any of the these three circumstances. In fact, there is little difference in overall mortality among cohort members compared to what might be expected based on mortality rates in the same region over the same period of follow-up, and no evidence to suggest that cohort members born in the years of the peak radiation releases from Hanford experienced higher than expected overall mortality.

An alternative but related explanation of how the loss of deceased members of the cohort could attenuate a dose-response might be that those who died were somehow more likely to have developed thyroid disease had they lived (sometimes referred to as a "healthy survivor" effect), or perhaps died with undiagnosed or unrecognized thyroid disease. However, in order for such explanations to contribute to or account for the absence of a dose-response, it must be assumed that those who do not survive experienced high or at least appreciable doses. Although it proved impractical to estimate individual doses for the deceased in this study, a number of additional analyses were undertaken among subgroups of people defined by cause of death, year of death, area of birth, and time of birth in an attempt to investigate patterns of mortality that might conceivably be related to thyroid dose. Mortality in excess of that expected occurred primarily at very young ages, concentrated in causes related to the perinatal period, but the excess was apparent for deaths that occurred prior to the beginning of Hanford operations, and were similar in magnitude to the excess seen for deaths that occurred in 1945 or later. This would argue against the cause of such excess at young ages (or conditions of the perinatal period) to be related to exposures from Hanford operations. Similarly there was little evidence that any excess mortality was concentrated in people more likely to experience higher dose based on geography. Finally, there was no indication that deaths were concentrated in categories that might be related to the development of the outcomes under study, and there was no mention of thyroid diseases on any of the death certificates. Thus, although it is not possible to know whether those who died had higher doses and might have been more likely to develop thyroid diseases had they lived, or had unrecognized thyroid disease at the time of their death, there is no indication of such based on examination of the data available.

In summary, a total of 3440 (66.2%) of the 5199 individuals initially selected for inclusion in the HTDS cohort were evaluable and provided data for the analysis. The proportion of those originally selected who attended a clinic and were evaluable was remarkably uniform across the factors that defined the selection: sex (males 64.1%, females 68.3%), year of birth (1940: 67.3%, 1941: 69.5%, 1942: 69.3%, 1943: 66.6%, 1944: 65.3%, 1945: 63.0%, 1946: 66.2%), and geostratum (Richland: 64.9%, Pasco/Kennewick: 64.8%, Walla Walla City: 64.1%, Benton County: 65.2%, Franklin County: 63.7%, Walla Walla County: 71.7%, Okanogan: 65.9%, Ferry/Stevens: 63.9%, Adams: 73.8%). Thus, although the final dose-response results are based on approximately two-thirds of the people originally identified for study, it appears that the degree of loss of individuals from the group was relatively uniform across subgroups defined by sex, year of birth, geographic area of birth, and geographic area of current residence. There is no indication that people were less likely to participate because they had thyroid disease, and in more general terms, illness was infrequently given as a reason for non-participation. Further, there is no indication of a substantial loss due to mortality in ways that are likely related to both exposure (dose) and the development of any of the outcomes of interest (i.e., in ways that would substantially affect the estimates of dose-response). Although one cannot rule out the possibility that the dose-response results might be biased in some way as a result of non-participation by nearly one-third of the cohort, no patterns of non-response or loss to follow-up are apparent from the data available that would suggest such is the case. In order for such a bias to have an important influence in producing the pattern of results seen in the HTDS (lack of a dose-response), one would have to postulate that people who did not participate were more likely to have one of the outcomes under study *and* to have received higher doses. As noted above, there is no evidence of such selection bias in the HTDS cohort.

C.2. Factors Related to Outcome Definition

An important element of a cohort study such as the HTDS is that the outcomes of interest are ascertained in a comprehensive and unbiased manner. That is, it is important that all cases of a given outcome are identified, and that the identification of cases is not influenced by or related to exposure or dose. The clinical component of the HTDS was designed to ensure that such was the case. Because of the long time period between the Hanford exposures and present day, and because the thyroid diseases under study can often be difficult to diagnose or even go undetected, it was felt essential that each participant undergo a thorough examination and evaluation for the presence of each of the outcomes under investigation as part of their participation in the study. Great care was taken to ensure that each person received the most complete evaluation possible by using highly experienced thyroid specialists. Further, two different physicians examined each participant separately, consulted with each other, and reached agreement on their findings before the participant left the clinic. State of the art technology was used in the form of thyroid ultrasound to help ensure that all thyroid nodules were identified. Nearly all participants who attended a study clinic completed all aspects of the evaluation, including providing a blood sample for laboratory tests and undergoing a fine needle aspiration biopsy when recommended. Analyses of the "pathways to diagnoses" of thyroid cancer, benign thyroid nodules, and nodules suspicious for follicular neoplasm demonstrated that the numbers of such cases were increased by the comprehensive clinical evaluation provided to each participant. Given this design, and the success experienced in carrying out the clinical component of the study, it is felt that the ascertainment of outcomes in the cohort is essentially complete. It is highly unlikely that substantial numbers of cases of any of the primary outcomes of interest were undetected, or that there is any substantial misclassification of outcomes.

The study was also designed to try to minimize the possibility that the physicians or sonographers could be influenced in their evaluation by knowledge of the participant's possible level of exposure to Hanford radiation. As outlined in section V.F.2.d, a number of measures were taken to prevent this from happening. At the clinic, participants were instructed not to make the physicians or sonographer aware of any personal circumstances that would suggest what their radiation exposure history might be. They were also asked not to wear clothing items that might provide any such indication. A variety of clinic locations were used, and participants were scheduled into clinics in a way that purposely *did not* correspond to prior residence history or the likelihood of exposure. Thus, when an individual physician examined a participant, he had no knowledge of what that particular participant's past history was in relation to the Hanford radiation releases (or any other potential radiation exposures). The same was true for the sonographer. As a check to see whether these precautions were effective in blinding the physicians to possible exposure, each physician was required to indicate at the conclusion of their evaluation whether they had any indication of possible exposure for that individual. In only 15 instances (of the 3440 living evaluable participants) did the physician suspect some knowledge of past exposure. Precautions were also taken to blind the physician reviewers of past medical records to any mention of radiation exposure. As described elsewhere, this was done in a manner that made it impossible for the reviewer to know for any given medical record whether there was any indication of previous exposure to radiation (either from medical or environmental sources). In summary, based on the success of the various approaches used, it is not likely that the determination of outcomes was influenced in any substantive way by knowledge of exposure.

C.3. Factors Related to the Estimation of Thyroid Radiation Dose

Just as it is important to accurately define outcomes, it is critical to accurately classify study participants according to exposure or dose. In this study, substantial misclassification of study participants according to radiation dose would tend to attenuate any true dose-response relationship (i.e., bias the estimate of effect towards the null). One approach to minimizing the likelihood of substantial exposure misclassification in a study such as this one where dose is estimated (reconstructed) based on historical information is to utilize individual-level information as much as possible to "tailor" each individual's estimate of dose to his or her own specific circumstances. The HTDS was designed from the beginning to use this approach. The cornerstone of the method was to elicit detailed information for each respondent regarding those factors most crucial in determining thyroid radiation dose from Hanford, and to use that

information to estimate an individual dose for each person. This was difficult to do because of the level of detail required, the long period of time that has elapsed since the exposures, and the fact that participants were young children during the time period that is most relevant for estimating dose. A considerable effort was made to structure the collection of individual information in a way that would enhance a person's ability to recall the information accurately by using a cognitive approach to interviewing, and to do so in a manner that would not be biased by the participant's knowledge of thyroid disease status. The administration of both the CATI and In-Person Interviews prior to the clinical evaluations probably aided in avoiding bias in recall to some extent. However, there is no way to directly assess the degree of potential misclassification of exposure that occurred using the approaches taken in this study.

Therefore, we repeated all of the analyses using alternative methods of assigning exposure to see if the results changed in any substantial way. First, we developed two alternative dose schemes that maintained an individual level dose estimate for each participant, using the HEDR models to estimate dose. The primary analyses were based on doses estimated using individual residence histories, individual responses to the CATI (or Expanded In-Person Interview), and HEDR default values when CATI responses were not available. The first alternative individual dose scheme used individual residence histories, and HEDR defaults exclusively (that is, no data from CATI or Expanded In-Person Interviews). The second alternative dose scheme was the same as the primary scheme, but HTDS default values were used when CATI responses were not available instead of HEDR default values (with the exception of consumption other than milk for Expanded In-Person Interviews, for which HEDR defaults were used). These HTDS default values for food and milk consumption data were defined based on the experience of the participants in the HTDS for whom a completed CATI interview was available. None of the dose-response results for any of the outcomes changed appreciably from the primary results using either of these alternative methods of estimating individual thyroid dose. This provides some assurance that the absence of a dose-response found in the primary analyses is not due to misclassification of exposure introduced by difficulties in recall from the distant past.

Second, two alternative representations of exposure were defined which were independent from the HEDR dosimetry system altogether, and therefore did not use the HEDR models to estimate individual radiation dose. One was simply the geostratum used to define the sampling frame for selecting the cohort (i.e., the mother's usual place of residence at the time of the participant's birth as determined from the participant's birth certificate). Although this is clearly an imperfect surrogate indicator for Hanford radiation dose, and does not take into account individual circumstances (e.g., movement patterns and dietary habits), it might provide at least a crude way to distinguish people more or less likely to have received substantial exposures.

For the primary definition of each outcome, analyses were conducted to see whether there was heterogeneity of outcomes across geostrata, and whether the proportion with the outcome in the two geostrata defined by Okanogan and Ferry/Stevens counties was different than that in the remaining seven geostrata. In summary, there was little evidence of significant heterogeneity in the cumulative incidence of any of the outcomes across all geostrata. Those outcomes showing the greatest degree of variation across geostrata were benign nodules, any thyroid nodules, any thyroid UDAs, and palpable thyroid UDAs.

Of more interest was the generally consistent finding that the proportion of participants with a given outcome was somewhat higher in the Okanogan and Ferry/Stevens geostrata than in the other seven geostrata. This pattern was apparent for the most part across all primary outcomes, although for those with very few cases (e.g., thyroid cancer, simple goiter, Graves disease, hyperparathyroidism) there was very little statistical power to evaluate the relationship. Insofar as geostratum serves as a surrogate indication of radiation exposure (and dose), and the underlying hypothesis is that radiation exposure from Hanford is associated with an increase in the thyroid disease outcomes under study, these results were quite unexpected because the Okanogan and Ferry/Stevens geostrata were defined in an attempt to identify people who were likely to have been relatively *unexposed* to Hanford radiation releases. Indeed, according to the individual dose estimates derived using the HEDR models, it appears that the sampling strategy was successful in that regard because the average doses for living evaluable in area participants in these two geostrata were the lowest of all nine geostrata (see Table IX.B-4, section IX.B: Okanogan, 11 mGy; Ferry/Stevens, 36 mGy).

It is not readily apparent why the cumulative incidence of the thyroid diseases under study would be slightly higher among people born in these three counties. Based on individual dose estimates that account for a person's movements and lifestyle, it appears that those selected from the Okanogan and Ferry/Stevens geostrata have the *lowest* doses in the cohort. There is also no evidence that this group is unusual in terms of selection or participation in the study, or ascertainment of disease status. Further, all of the analyses by geostrata were adjusted for differences by sex and age at examination. It is also difficult to imagine that some other aspect of birth, early life, or living in these areas is related to the risk of developing thyroid disease, as the apparent effect is seen across *all* outcomes (including hyperparathyroidism and thyroid UDAs). One would have to postulate that such an influence is related to all the different forms of thyroid disease included in this study, which seems exceedingly unlikely. A possible exception might be iodine deficiency. Geographical differences in the distribution of iodine intake (e.g., endemic goiter belts) could result in geographic differences in the rates of one or more of the thyroid diseases under study.

As described in section IV above, there is very little information available describing either estimates of soil iodine concentrations or iodine intake on a geographical basis. Probably the most useful data in this regard are those reported by Oddie et al. (153). He reported estimates of average dietary iodine intake derived from thyroidal radioiodine uptakes in approximately 30,000 euthyroid subjects in 133 locations throughout the United States. Although average daily iodine intake varied considerably throughout the United States (from 240 to 740 micrograms per day), the Pacific Northwest was relatively uniform in the distribution of daily intake estimates. Mean values were reported for fifteen areas in the Northwest centered by two degrees latitude and longitude (approximately 140 by 120 miles). All values in the six HTDS Pilot Study counties were between 345 and 379 micrograms per day (a very narrow range compared to the overall distribution of values). These findings provide some evidence that iodine intake was adequate and relatively uniform in the past in the areas from which study participants were selected. As such, they suggest that iodine deficiency is not a likely explanation of the relatively higher proportions of thyroid disease among people selected from the Okanogan and Ferry/Stevens geostrata.

Nevertheless, because the cumulative incidence of disease was consistently higher in the Okanogan and Ferry/Stevens geostrata in a manner possibly related to dose, it was decided to repeat the primary dose-response analyses omitting people born in these two geostrata. If thyroid disease rates were truly elevated in the population from which people in these geostrata were selected, and such people tended to have lower Hanford doses, the dose-response analyses might be biased toward the null (i.e., the dose-response might be underestimated). Generally, the effect was to increase the regression coefficient (slope of the dose-response). However, none of the changes were substantial enough to suggest a significant dose-response relationship. The largest changes were for the outcomes related to thyroid UDAs. For any thyroid UDAs, the regression coefficient increased from 0.031 per Gy to 0.046 per Gy, and the p-value changed from 0.21 to 0.11. Thus, although the effect of excluding participants from these geostrata had the anticipated effect on the dose-response results, it did not materially change the overall findings or conclusions. It should be emphasized that analyses that excluded the Okanogan and Ferry/Stevens geostrata were not included in the original analysis plan, but were conducted only after the higher cumulative incidence rates in these two geostrata were observed. Given the data-driven nature of this additional analysis, there is no evidence to suggest that the somewhat higher cumulative incidence of disease in the Okanogan and Ferry/Stevens geostrata led to a significant underestimate of the dose-response for any of the primary outcomes under study.

The second alternative representation of exposure which did not use the HEDR models to estimate individual dose was based on the assumption that two factors are particularly important in determining radiation dose from Hanford: a person's residence history and history of milk consumption. A dichotomous representation of possible exposure (high, low) was defined based on this information. For this analysis, the high exposure group was defined to include those living evaluable participants who:1) were born prior to July 2, 1945;2) lived for at least 180 days in Benton, Franklin or Adams counties (excluding Richland) during 1945; and 3) consumed on average at least one serving of milk per day during 1945. The low exposure group was defined to include: 1) all out-of-area participants (OOA); 2) participants who lived only in Ferry, Stevens or Okanogan counties or OOA in 1945 and who never lived in Benton, Franklin or Adams counties between 1946 and 1951 inclusive;3) participants born in 1946 who never lived in Benton, Franklin or Adams counties between 1946 and 1951 inclusive; or 4) participants who lived outside of

Benton, Franklin or Adams counties from the later of the participant's birthday and 12/15/44, until 12/31/51, and consumed on average less than one serving of milk per day in 1945 (includes only participants with CATI as the dose source).

Using this dichotomous representation of possible exposure (high, low) and the primary definition of each outcome, analyses were conducted to see whether the cumulative incidence of each outcome was greater among those in the high dose category relative to the low dose category. In summary, there was no evidence of a significant relationship between exposure, as represented in this manner, and the cumulative incidence of any of the outcomes. There was a slightly higher proportion of participants with thyroid UDAs in the high group relative to the low group (50.3% vs. 47.4%), but not significantly so ($p = 0.10$), and this relationship was somewhat more pronounced when the analysis was restricted to nonpalpable focal thyroid UDAs (41.5% vs. 37.6%, $p = 0.079$).

Although this approach for assigning exposure is also crude, it incorporates at least some of the information about each individual's circumstances that is thought to be important in the determination of dose. As such, this surrogate indicator should be somewhat more capable of distinguishing people who received relatively higher doses from those who received relatively lower doses than the simple geostratum designation. If so, it nevertheless does not provide any evidence of a statistically significant association between higher Hanford radiation dose to the thyroid and an increase in any of the primary outcomes under study.

A limitation of the dosimetry system available for this study was its inability to calculate dose estimates for participants who did not live within the HEDR domain between December 1944 and the end of 1957. As a result, the primary dose-response results of this study refer to dose received while living in the HEDR domain between December 1944 and the end of 1957. Individual dose estimates could not be calculated for the 249 participants who lived outside the HEDR domain during that period, the so-called "out-of-area" participants. It is reasonable to assume that the out-of-area participants received generally low doses. In particular those who lived only at great distance from Hanford during this time period probably received virtually no dose from Hanford. However many out-of-area participants lived in places not far outside the HEDR domain. It is probably inappropriate to simply assume that such people received no exposure from Hanford.

Therefore, scoping analyses were performed to assess whether inclusion of the out-of-area participants in the primary analyses, had that been possible, might have substantially changed the dose-response results. These analyses assigned crude estimates of a dose for the out-of-area participants, based on residence during the 1944-1957 exposure period. Out-of-area participants who lived in the four states or two Canadian provinces closest to Hanford were assigned doses of either 0 mGy, or the highest dose that they would have been assigned had they lived on the border of the HEDR region in the direction of the state or province (which would likely overestimate the dose they could have actually received), depending on their disease outcome status. Those who lived outside that four-state/two-province region were assigned doses of 0 mGy. A scoping analysis of each disease outcome was then performed in which all out-of-area participants with the outcome were assigned their "border dose," while those without the outcome were assigned 0 mGy. This imposes a strong dose-response relationship among the out-of-area participants. However when the in-area and out-of-area participants were combined in these scoping analyses, there were no important changes in the estimated dose-responses. This was true even in the analysis of thyroid cancer, for which five of the 19 cases based on HTDS or prior histology were out-of-area participants. A second scoping analysis assigned doses in the reverse order, so that out-of-area participants with the outcome received a dose of 0 mGy and those without the outcome their "border dose." This did not materially change the estimated dose-response for any outcome either.

It is perhaps not surprising that neither of the scoping analyses which included the out-of-area participants had much impact on estimated dose-responses, since the out-of-area participants comprised only 7.2% (249/3440) of the living evaluable participants. Moreover the crude dose estimates that they were assigned ranged from 9 to 48 mGy, well below the mean dose of 174 mGy observed for the 3191 in-area participants.

In summary, a number of attempts were made to use alternative approaches for characterizing study participants in terms of their exposure to Hanford radiation, including both alternative quantitative and qualitative schemes. This was done so that the investigation of a possible relationship between Hanford radiation exposure and thyroid disease would be as complete and comprehensive as possible, would rely on multiple types and sources of data, and would not be limited to only one dose assessment approach and the associated assumptions. It was recognized from the beginning of the study that there would be limitations in the quantitative dose estimation program developed by HEDR, and that alternatives based only on residence location would provide crude indicators of exposure at best. The decision to use both approaches, and to look for consistency in results, was felt to provide a more thorough assessment of a possible relationship between radiation exposure and thyroid disease. Analyses of all of the primary outcomes were repeated for each alternative approach. None of these analyses produced evidence of a statistically significant relationship between any of the primary outcomes and exposure to Hanford radiation (or dose). The principal findings of the primary analyses using individual doses estimated by the HEDR dosimetry system were not materially changed by any of these alternative analyses. In addition, all primary analyses were repeated using the arithmetic mean, and the geometric mean, of the 100 dose realizations for each participant rather than the median dose estimate. This did not change the results. All primary analyses were also conducted fitting sex-stratified linear-quadratic and logistic dose-response models. The addition of the quadratic term did not significantly improve the fit of the dose-response model for any of the outcomes under study, and neither the linear-quadratic or logistic models provided any evidence of a significant radiation dose-response.

For many of the disease outcomes, the numbers of cases among participants with the highest dose estimates tended to be relatively low. As a result, estimated slopes of the dose-response relationships were slightly, though not significantly, negative for these outcomes. Additional analyses were performed to assess whether these results might be unduly influenced by the relatively small proportion of participants with the highest doses. In particular, the primary analyses of disease outcomes were replicated twice: once excluding participants with estimated doses above 1000 mGy, and a second time excluding those with doses above 400 mGy. The first alternative analysis had very little impact on the fitted dose-response models. A somewhat stronger impact was seen in the analysis that excluded participants with estimated doses over 400 mGy. For most disease outcomes, the slope of the dose-response tended to be greater when based on the limited set of participants, although in general the increases were not large enough to suggest a statistically significant dose-response. For two outcomes, the exclusion of participants with estimated doses over 400 mGy increased the estimated slope of the dose-response substantially. For nonpalpable focal thyroid UDAs the estimated slope increased from 0.027 per Gy ($p = 0.23$) to 0.228 per Gy ($p = 0.003$). For diffuse thyroid UDAs the estimated slope increased from 0.029 per Gy ($p=0.14$) to 0.146 per Gy ($p=0.005$).

While the magnitudes of the dose-responses for these two ultrasound outcomes excluding participants with estimated doses over 400 mGy are considerably larger than the estimates among all study participants, the statistical significance of these results must be interpreted with caution. First, this is a secondary, exploratory analysis that only shows a significant effect when people with the *highest* thyroid doses are excluded. Second, it should be kept in mind that this result was found in the context of conducting many secondary and alternative analyses and significance tests. Third, such abnormalities are quite common. Numerous investigations in populations throughout the world have reported that 20-50% of individuals may have one or more such findings on ultrasound examination. Fourth, and perhaps most importantly, the health significance of nonpalpable focal and diffuse thyroid UDAs is unclear. Whereas thyroid UDAs that are palpable can be classified as thyroid disease, the high prevalence of those that are not palpable may not represent clinical disease. Since no dose effect was detected for recognized thyroid disorders such as thyroid cancer, benign thyroid neoplasia, and hypothyroidism, it would seem unlikely that the focal and diffuse ultrasound findings would be clinically significant. Could these ultrasound findings represent *subclinical* thyroid disease? In other words, very mild abnormalities that do not cause symptoms but might be destined to become clinical disease over time? If this were true, one might expect to see 2 types of dose-response results in the HTDS: an increase in the number of ultrasound abnormalities with increasing dose, and an increase in the risk of having an ultrasound abnormality of a particular size with increasing dose. The HTDS examined both of these possibilities. First, there was no relationship found between the number of ultrasound abnormalities on a participant's ultrasound scan with increasing dose.

Second, there was no increased risk of having larger, focal ultrasound abnormalities (maximum size 5mm, maximum size 10 mm, or average size at least 15 mm) with increasing dose. Thus, these results do not suggest that these ultrasound findings represent early manifestations of thyroid disease. In summary, based on the above factors, it would seem very unlikely that the dose-response seen for nonpalpable focal and diffuse ultrasound abnormalities, found only after secondary, exploratory analyses, and only after excluding participants with the highest doses, truly represents a significant dose effect in the HTDS.

C.4. Potential for Confounding or Effect Modification

Although relatively few factors have been well established as important in the etiology of the thyroid diseases under study, an attempt was made to collect as much information as possible from study participants regarding aspects of their personal history and lifestyle that might potentially influence the risk of developing thyroid disease. As described in section VIII, this information was used to construct several variables for inclusion as covariates in the dose-response analyses. Analyses were conducted for all outcomes with sufficient numbers of cases to evaluate whether any of these factors confounded the relationship between the outcome of interest and estimated Hanford radiation dose, or whether any dose-effect was modified by levels of the factor (e.g., for sex, whether the effect was different in males and females).

None of the covariates investigated materially changed the estimates of the dose-response for any of the outcomes under study. There was no evidence of confounding by any of the factors, nor was there any evidence of effect modification by any of the factors assessed. This included the covariate reflecting exposure to radiation from the Nevada Test Site. These rather extensive analyses provide no evidence that there is a significant dose-response for any of the outcomes under study, or evidence of a significant dose-response among subgroups of participants defined by any of the covariates investigated.

C.5. Statistical Power of the Study

Of critical importance in the interpretation of these results is the ability of the study to detect an increase in disease risk if it is present, i.e., the statistical power of the study. In order for the findings of an absence of an effect to be very meaningful, there must be adequate statistical power to detect an effect of the magnitude that might be expected based on existing knowledge, and that is relevant and meaningful to the population exposed. As described more fully in section VIII, the HTDS was designed to have relatively high power to detect a positive dose-response as small or smaller in magnitude than any existing published findings regarding each outcome. These projections of study power, which were based on the results of the Pilot Study, were actually exceeded in the Full Study (as shown in Table IX.B-14 above). Nevertheless, because uncertainties in the individual dose estimates could be expected to reduce study power, we undertook a simulation analysis to estimate the impact on study power of incorporating such uncertainties in the dose estimates (see section IX.B-4). Although the effect of dose uncertainty was, as expected, to reduce the statistical power of the study, the reduction was modest. Even after accounting for uncertainty in doses, the HTDS had greater than 80% power to evaluate each of the hypotheses originally specified.

To interpret the study's power properly, it is important to consider not only the level of power, but also the size of the dose-response effect for which that power is obtained. As described in section IX.B.4 above, after accounting for the impact of dose uncertainty, the study's one-sided tests at critical level $\alpha = 0.05$ had estimated power of about 85% to 86% to detect linear dose responses corresponding to relative risks (average for both sexes) of 2.04, 1.30, and 1.05 at the study participants' average dose of 174 mGy, for the exemplary outcomes with low (thyroid cancer), intermediate (any thyroid nodule), or high (thyroid UDA) background rates, respectively.

For comparison to results of other studies, the magnitudes of radiation effects can be expressed as the relative risks at 1000 mGy (1 Gy). For the low background rate example of thyroid cancer, a slope of 2.5% per Gy, for which HTDS had about 86% power (Table IX.B-16 above), corresponds to a relative risk

(average of both sexes) of 6.95 at 1 Gy. This is a substantially smaller effect than that observed in the Utah Thyroid Study, for which the relative risk was estimated as about 25 at 1 Gy after accounting for dose uncertainties (67). A recent analysis suggested that the adjustment should perhaps be smaller: Mallick and colleagues analyzed the Utah Study's data concerning thyroid neoplasms and concluded that the estimated relative risk at 1 Gy should be approximately doubled, rather than tripled, to account for dose uncertainties (165). Assuming this conclusion applies to thyroid cancer, the estimated relative risk would be about 17 at 1 Gy. The HTDS clearly had adequate statistical power to detect an effect of this magnitude. For example, after accounting for dose uncertainty there was an estimated 92% power to detect a linear dose-response with a slope of 3.5% per Gy for thyroid cancer (Table IX.B-16 above), which corresponds to an average relative risk (both sexes combined) of 9.33 at 1 Gy, well below the estimated effect from the Utah Study.

D. Comparison of Results with Findings in Other Populations Exposed to Radiation

Although there is a substantial literature regarding the role of ionizing radiation in the induction of thyroid disease in humans, the findings reported to date do not provide a clear and consistent characterization of the relationship between radiation exposure and risk. This is due in part to the fact that a number of factors are probably important in determining risk: the type of radiation, the dose received, the rate at which the dose was received, a person's age at the time of exposure, a person's age at the time of disease occurrence, and iodine deficiency. Thus, in comparing the results of the present study with those published, it is important to keep in mind the characteristics of the Hanford exposures and the basic design features of the HTDS. The exposure was environmental, and occurred over a period of up to approximately 13 years, although much of the dose was delivered in a considerably shorter period of time, and many people may have received most of their dose over periods of several months. The design of the HTDS resulted in a study group that consisted of people who were young children (under age 5) at the time of the peak exposures, and follow-up occurred over a period of up to more than 50 years. Radiation dose to the thyroid from ^{131}I was estimated for each individual, based on historical reconstruction of events. Estimated doses for the study group were relatively low (median dose = 97 mGy, mean dose = 174 mGy). Thus, it is within this context that the present results are considered in relation to the published literature. The primary goal of this comparison is to evaluate how well the current findings "fit in" with what is currently known about radiation-induced thyroid disease. To the extent possible, specific analyses have been tailored to be as comparable as possible to published results, for the explicit purpose of direct comparison.

A more detailed presentation of the published literature is contained in sections II.B through II.D above. It is not the intent to repeat those descriptions here, but rather to highlight the principal points for comparison with the HTDS findings. There is clear evidence from a number of studies that people exposed to external sources of gamma radiation or x-rays are at an increased risk of developing thyroid neoplasia. There is also evidence to suggest that the risk is greater for people exposed at younger ages. Most of this evidence comes from studies of people treated medically with radiation, and from studies of the survivors of the atomic bombings in Japan. Thus, in both circumstances, doses were generally considerably higher than those in the HTDS, were generally delivered at a much higher dose rate, and reflect external exposures. Nevertheless, one study of children irradiated for *tinea capitis* provides some evidence of an increased risk associated with much lower doses (average dose = 90 mGy).

Of much more relevance to the Hanford circumstances are studies which have evaluated the effects of exposure to radioactive iodine. Unfortunately, much less information is available in this regard, especially in human populations. Two types of information exist: findings based on people exposed in medical settings, and findings based on people exposed environmentally. People exposed therapeutically to radioactive iodine (primarily for the treatment of Graves disease) generally received very high doses. However, there is no clear evidence that such exposures result in a subsequent increase in thyroid neoplasia. People exposed for diagnostic purposes generally received much lower doses, but the doses are still relatively high compared to the Hanford doses (typically 500 – 1000 mGy). There is no convincing evidence that exposures at these levels result in increased thyroid neoplasia. Although the rates of thyroid cancer were elevated in some of the above studies, the authors concluded that the increase was more likely related to the underlying thyroid disease than to the radioiodine exposure.

Information regarding the effect of environmental exposure to radioactive iodine comes from studies of three principal populations: people exposed to fallout from atmospheric nuclear testing in the Marshall Islands in the 1950s, people exposed to releases from the Chernobyl Power Station accident in the Former Soviet Union in 1986, and people exposed to fallout from atmospheric nuclear testing at the Nevada Test Site in the 1950s and early 1960s. The experiences in the Marshall Islands and at Chernobyl are less directly comparable to the Hanford experience because the exposure in each instance consisted of a broader and different mixture of radionuclides, and the dose rates were relatively high (short time of exposure). Nevertheless, in the Marshall Islands there has been an increase observed in thyroid neoplasia associated with the more highly exposed areas, with doses much higher than those around Hanford. Around Chernobyl there has been reported a dramatically increased occurrence of thyroid cancer in young children. Unfortunately, there are no epidemiologic studies available with quantitative estimates of individual thyroid radiation dose from Chernobyl to better elucidate the nature of any dose-response in this regard. However, a number of attempts to estimate radiation doses on a population basis suggest that the doses were generally much higher than those around Hanford.

The study of people exposed to fallout from the Nevada Test Site, the so-called "Utah Study"(67,92), is probably the most comparable to the Hanford situation. The mean dose for all 3545 participants who were included in any phase of the Utah Study was 98 mGy, compared to 174 mGy for the 3191 living evaluable in-area HTDS participants. The maximum estimated thyroid dose in the Utah Study was 4600 mGy (2823 mGy for HTDS), although only 10 participants (0.3%) had estimated doses greater than 1000 mGy (24 or 0.8% for HTDS). However, there was likely a greater contribution from short-lived radioiodines and external radiation in the Nevada Test Site exposures compared to exposures at Hanford. Moreover, the participants in the Utah Study received most of their dose in short time periods after one or more test detonations. In contrast, most Hanford exposures were continuous and prolonged over months or years. A statistically significant dose-response was reported for total neoplasms (benign follicular neoplasms and thyroid cancer) in the 2473 participants who were included in the Utah Study's analysis of period prevalence between 1965 and 1986. Based on the linear relative risk model, the excess relative risk was estimated to be 0.070 per mGy, with unadjusted 95% confidence interval ranging from 0.007, 0.33 per mGy ($p = 0.019$). A relative risk of 3.4 (95% confidence interval 0.5, 26.9) was reported for all thyroid neoplasms for people with a dose of greater than 400 mGy. Although there were positive dose-responses for thyroid cancer and total nodules when these two outcomes were analyzed separately in the Utah Study, they were not statistically significant ($p = 0.16$ and 0.096, respectively).

Analyses that adjusted for the effect of dose uncertainties were also performed for the Utah Study. The dosimetry model and the approach to estimating doses for the Utah Study were, broadly speaking, similar to the HEDR model and HTDS approach. The size of the dose uncertainties was summarized as follows for the Utah Study: the geometric standard deviations (GSDs) for over 90% of the Utah Study participants were between 1.75 and 3.75 (92). This is generally similar to the magnitude of dose uncertainties for HTDS participants, whose GSDs ranged from 1.56 to 5.42, with a mean of 2.18 (see Section IX.B-2). The Utah Study investigators performed additional analyses in an attempt to adjust for the effect of dose uncertainties, which yielded adjusted estimates of the dose-response coefficients that were roughly three times greater than the unadjusted estimates. The standard errors of the estimates also increased in approximate proportion to the estimates, so the statistical significance of the dose-responses was essentially unchanged (67,92). A recent reanalysis that attempted to account for the correlation of uncertainties in the Utah Study's dose estimates suggested that the adjustment should in fact have been somewhat smaller (165).

A number of other thyroid diseases investigated in the HTDS have also been linked to radiation exposure. It is clear that exposure to external gamma radiation, x-rays, or ^{131}I at high doses increases the risk of developing hypothyroidism. There is no evidence, however, that exposure to radioactive iodine, at lower doses similar to those estimated in the HTDS cohort, has the same effect. The HTDS found no statistically significant evidence of such an effect. This is consistent with the results of the Utah Study, which found no evidence that the risk of hypothyroidism increased with increasing estimated dose from the Nevada Test Site's fallout (92).

Two recent studies have suggested that autoimmune thyroiditis may be radiation-induced. These findings come from studies of the Japanese atomic bomb survivors and people exposed around Chernobyl. As indicated above, they reflect very different types of exposures than at Hanford: external sources of exposure, higher doses, and higher dose rates. Nevertheless, for comparison purposes, we conducted an additional dose-response analysis that would correspond more directly to the analysis reported by Nagataki et al. (28). For that analysis we defined autoimmune thyroiditis to include only those cases associated with non-iatrogenic permanent hypothyroidism (see section IX.H above). The results of this analysis provided no evidence of a significant dose-response (slope of the dose-response = 0.001 ± 0.015; p-value = 0.48). It should be noted, however, that there were 161 cases of autoimmune thyroiditis in the HTDS cohort according to this definition (cumulative incidence of 4.7%), which is considerably higher than reported by Nagataki et al.. They report 27 clinical cases (1.0%) and 38 subclinical cases (1.5%) in their group of 2587. Unfortunately, insufficient detail is provided in the published paper to discern exactly how their cases were defined. Thus, it may be that the results of our alternative analysis are not truly comparable to those of Nagataki et al., and the reason that the HTDS was not able to confirm their findings may be in part due to the use of different criteria for the diagnosis.

The outcomes of hyperthyroidism, thyroiditis, and goiter were also investigated in the Utah Study, and for none of these were statistically significant dose responses observed (92). While these findings, taken at face value, appear to be consistent with the results of the HTDS, it is important to recognize that the definitions and diagnostic criteria used for these outcomes differed somewhat between the two studies.

There is also reasonably clear evidence that exposure to head and neck irradiation in childhood increases the risk of developing hyperparathyroidism. However, this evidence is based on situations in which the exposure was due to external sources and the doses and dose rates were generally quite high. There has been no convincing evidence in humans regarding the effect of exposure to radioactive iodine. However, it is estimated that the radiation dose to the parathyroid glands is less than that of the dose to the thyroid from a given exposure to radioactive iodine. Thus, given the thyroid dose distribution in the HTDS, it would be expected that parathyroid doses to members of the HTDS cohort were very low.

Relatively little is known about whether ionizing radiation causes an increase in thyroid abnormalities detected by ultrasound prior to the development of clinical disease. Schneider reported that exposure to external radiation was associated with a high prevalence of thyroid UDAs (117). In 54 exposed individuals followed in his study, 87% (47/54) had abnormal ultrasound scans. In this cohort, radiation exposure was due to external sources. The authors concluded that 1) thyroid nodules continued to develop in radiation-exposed individuals many years after exposure and 2) although thyroid UDAs were quite common in the general population, they were more prevalent in radiation-exposed populations.

Other studies have also suggested that thyroid UDAs are more common in exposed populations. Antonelli compared ultrasound scans among 50 hospital workers with occupational radiation exposure (external radiation) in a hospital setting to 100 controls without such exposure (118). Thyroid UDAs were detected in 38% of the exposed people and only 13% of the controls. Similarly, Sugenoya and colleagues (114) compared 299 children who were exposed to Chernobyl radiation to 323 children who were unexposed. Although none of the children in either group had palpable abnormalities, 34 of the exposed (11.4%) had thyroid UDAs compared to 4 unexposed children (1.2%).

There are no published estimates of the risk of developing thyroid UDAs as defined by the HTDS in relation to exposure to radioactive iodine.

Thus, in considering the HTDS dose-response findings in the context of the literature on radiation-induced thyroid disease, it is important to keep in mind the principal differences between the Hanford exposures and those in other populations that have been studied. The Chernobyl exposures occurred in a relatively short period of time and were substantially greater. Doses in populations around Chernobyl studied to date have generally been higher, and dose rates were much higher than at Hanford. The mix of radionuclides released was also different from Hanford, and there is some evidence that iodine deficiency may be contributing to the excess in thyroid cancer observed thus far. The Marshall Island experience is somewhat similar to the Chernobyl experience, insofar as doses were generally much higher and dose rates

much higher than at Hanford. The mix of radionuclides was also more varied than at Hanford. The exposures in Utah from the Nevada Test Site were also due to a broader mix of radionuclides than at Hanford, although resulting doses were similar to those at Hanford. The dose rate for any given individual in the Utah study was also relatively high, compared to that at Hanford, even though the exposures occurred over many years. That is because the exposures resulted from individual nuclear tests, which delivered the radioactive contamination in discrete, short periods of time. In contrast, exposures at Hanford were relatively constant over time (although concentrated in the early years of operation). Considered in total, the differences summarized above may largely explain why no dose-effects were observed in the HTDS analyses.

E. Comparison of the Occurrence of Thyroid Disease Outcomes With Other Findings in the Literature

The section above considered the thyroid disease dose-response results of the HTDS in the context of reported findings in other populations exposed to ionizing radiation. It is also important to consider the findings of the clinical component of the HTDS (the determination of thyroid disease outcomes) in relation to what is known about the occurrence of thyroid disease in other populations around the world. That is, how does the magnitude of thyroid disease occurrence found in the HTDS cohort (the cumulative incidence) compare with the levels of thyroid disease observed in other populations? Of particular interest is whether the occurrence of thyroid disease in the HTDS cohort is *greater* than has generally been found in other populations not exposed to ^{131}I from Hanford. If so, this might be considered evidence of a possible effect of Hanford radiation exposure, even in the absence of any dose-response relationships.

This is an exceedingly difficult question to answer because, as noted previously, the magnitude of thyroid disease rates observed in any given population depends upon a number of different factors. First, the recognition and diagnosis of thyroid disease in a population depends to a large extent on how aggressively one looks for disease. Sometimes referred to as the "screening effect", a concerted effort to screen for a disease in a population, including the implementation of a comprehensive diagnostic protocol as part of a research study like was done in the case of the HTDS, will result in higher rates of disease than would be observed with normal medical care practices in the same population. This is particularly so for thyroid neoplasia, which may not result in clinical symptoms and therefore can remain undetected, or functional forms of thyroid disease such as hypothyroidism which may go unrecognized as thyroid disease because of non-specific symptoms. Second, the extent to which thyroid disease is identified in a population may depend on the diagnostic methods used or the criteria for diagnosis that are employed. For example, the use of thyroid ultrasound will substantially increase the level of nodular thyroid disease detected in a population compared to that found by physical examination (palpation) alone. Similarly, different thresholds for laboratory values used to define a case of hypothyroidism could result in apparent differences in disease occurrence that simply reflect differences in diagnostic definition. Such detection effects can be substantial. For example, there is direct evidence in the HTDS of a large "screening effect" for thyroid cancer. Twelve of the 20 cases of thyroid cancer among the 3440 evaluable study participants were detected as a result of the HTDS examinations, and 2 of the 12 cases were diagnosed by palpation only after the ultrasound scan was reviewed and the participants were re-examined. The resulting cumulative incidence for thyroid cancer was 2.5 times greater than what it would have been had it been based on cases identified through the normal medical care system.

Third, populations with different characteristics or different exposures which might affect the occurrence of thyroid disease can exhibit very different disease rates. For example, rates of most forms of thyroid disease are higher for females than males, and increase with increasing age. Thus, all other factors being comparable, two populations with different age and gender structures might exhibit very different rates of thyroid disease. Similarly, people living in an iodine deficient environment would likely have different rates of some forms of thyroid disease than people who are iodine sufficient.

Despite these substantial obstacles to making valid comparisons between the cumulative incidence of specific outcomes determined in the HTDS and estimates found in the published literature, we attempted

to assemble the most comparable information possible for the most important outcome categories studied. A summary of this information is presented in the subsections below, with special attention given to differences between specific studies and the HTDS which could account in part or entirely for differences in reported disease rates. Although admittedly imperfect, these data provide at least a frame of reference within which the cumulative incidence data from the HTDS can be evaluated.

E.1. Prevalence of Thyroid Cancer

The occurrence of thyroid cancer varies widely worldwide, is more common among females, and increases sharply with increasing age. Annual incidence rates have been reported to range from a high of 104 cases per million in women in Hawaii to a low of 14 cases per million in women in Poland (166). The age-adjusted annual incidence in the United States is 55 cases per million people (80 per million in women and 29 per million in men)(166). Further, the incidence of thyroid cancer in the United States has steadily increased over the last several decades, perhaps in part due to improved methods of diagnosis (166). Although it might be preferable to compare the occurrence of thyroid cancer in the HTDS cohort to that in other populations using incidence data, the retrospective nature of the HTDS design precluded us from accurately determining a date of diagnosis for each case, and therefore from calculating an incidence rate in the cohort.

It is possible to use incidence data to predict the cumulative incidence of thyroid cancer that might be expected in the HTDS cohort, although such predictions must be interpreted cautiously. In fact this was done at the beginning of the study to assist in developing the study design. As described in Appendix H of the HTDS Protocol (1), the cumulative incidence of thyroid cancer for the HTDS cohort was estimated using age- and sex-specific incidence rates from the Cancer Surveillance System (CSS), a population-based registry for the thirteen northwestern counties of Washington State. To account for the screening effect of the HTDS clinical examinations, the CSS incidence rates were multiplied by three, using a value suggested by the National Council on Radiation Protection and Measurements (45). The predicted cumulative incidence of thyroid cancer was 0.0068 (0.68%) for women and 0.0025 (0.25%) for men. These predictions are in good agreement with the observed values of 0.7% for women and 0.4% for men (see Section IX.C above). While this may be viewed as evidence that overall thyroid cancer rates for the HTDS cohort are not higher than expected, it must be recognized that incidence rates in the population covered by the CSS may differ from the background rates of the HTDS cohort, and that the factor of three assumed for the screening effect may not be appropriate for the HTDS clinical evaluation.

Unfortunately, there is very little information available regarding the prevalence of thyroid cancer in the general population. This is due primarily to two reasons. First, because the absolute frequency of incident cases is quite low, screening programs in the general population are not very feasible and are generally not considered an appropriate use of resources. Second, it can be difficult to discriminate between clinically significant thyroid cancer and that which does not adversely impact a person's health. The latter is usually referred to as occult or microscopic cancer.

There have been a number of studies of patients with thyroid nodules who are referred for surgery (167). Very high prevalence rates of thyroid cancer (5-24%) have been reported from these studies. However, such surgical series have a high likelihood of selection bias since such patients are usually referred because of high suspicion for thyroid cancer. Consequently, these studies almost certainly overestimate the true prevalence of thyroid cancer in the general population.

The best data for estimating the frequency of "occult" or microscopic thyroid cancer come from autopsy studies, where microscopic thyroid cancer is found in people who died of other causes. Crapo and Wang summarized a series of nine autopsy studies, performed from 1952-1977, which showed a mean prevalence of thyroid cancer to be 3.6% among 3744 cases (range of prevalence 0.45-13.0%) (167). These studies were chosen in part because they all were carefully performed, each examining 1-3 mm slices of thyroid tissue.

In contrast to clinically important thyroid cancer, most studies show that occult thyroid cancer does not seem to vary by age or gender. These studies also show that the correlation between prevalence of

occult thyroid cancer and mortality is poor. Countries such as Japan have a high prevalence of occult thyroid cancer but low mortality, whereas other countries have both low prevalence and low mortality. For example, Fukunaga reported a 24-28% prevalence of occult thyroid cancer from autopsy studies of Japanese and yet there is a low mortality rate from thyroid cancer in Japan (168).

In summary, there are no good estimates of thyroid cancer prevalence to which the cumulative incidence findings in the HTDS cohort can be compared. The prevalence estimates that are available are most certainly overestimates of what might reasonably be expected in the HTDS cohort, as they are derived from either patients referred for surgery, or from autopsy studies of occult cancer.

E.2. Prevalence of Thyroid Nodules

It is well known that thyroid nodules are a common finding in the general population (reviewed in 167). The primary determinant of the variation in prevalence estimates of thyroid nodules is the method of detection. Estimates vary widely, depending on whether the method of detection is palpation, ultrasound, or autopsy.

The oldest and most widely quoted study of thyroid nodularity in the general adult population is the Framingham Study, which began in 1948 and employed palpation as the method of detection (169). The initial cohort was composed of 5127 randomly selected individuals from the town of Framingham, Massachusetts who were given careful thyroid physical examinations to determine the prevalence of thyroid nodules. The age range was 30-59 and the geographical area was not felt to be iodine deficient. The criteria for a definite solitary thyroid nodule was one that was palpable by at least two examiners, while suspected nodules were those palpable by only one examiner. The average diameter of nodules was 1 cm. The prevalence of definite single nodules detected over a 5 year examination period was 1.9% (2.7% for females; 0.8% for males), while the combined prevalence of definite and suspected solitary nodules was 3.0% (4.6% for females, 1.1% for males). An additional 1.1% of the cohort had multiple palpable nodules (1.7% for females, 0.4% for males). Thus, of the total 5127 people examined, 218 people, or 4.2% had palpable thyroid nodules (6.4% for females, 1.5% for males).

A 15-year follow-up study of this cohort was subsequently published in 1968 (170). Of the 218 people found to have thyroid nodules in the initial survey, 139 people still had nodules which were unchanged at the 15-year follow-up. Of the remaining 79 people, 45 had nodules excised during the follow-up period (all were benign), 15 had died (none of thyroid related causes), and 19 had nodules that were excised prior to the initial survey (all benign). Of 4909 people who were free of palpable thyroid disease at the initial survey, 67 people (1.4%) developed new nodules during the 15 year follow-up. Although none of these new nodules were reported to have thyroid cancer, only 13 people actually had surgery; the remainder were thought to be clinically benign.

Thus, the cumulative incidence of palpable thyroid nodules at the end of the 15 year follow-up period in the Framingham Study was 5.6% (285/5127 people); for females the cumulative incidence was 8.1% (230/2845) and for males 2.4% (55/2282). Of the total 285 people with nodules, all were thought to be clinically benign. Although only 27% had surgical excision, none showed any evidence of malignancy**.** The initial study attempted to discriminate between solitary nodules and multiple nodules (73% were solitary), however the follow-up study did not and included all nodules in the prevalence data whether they were thought solitary or multiple. These estimates of nodule prevalence are probably the most comparable to the HTDS experience found in the world literature: they represent reasonably long-term follow-up, the age range at the end of follow-up is approximately 45-74, most people were examined by multiple physicians, the estimates include people with prior surgery, and the population under study is a randomly selected group.

A similar study by Whickham et al. documented the prevalence of thyroid disorders in 2779 adults who were age and sex matched to the British population (171,172). Although this study provides some of the highest quality information regarding thyroid dysfunction and autoimmune thyroid disease in an unselected population (see below), the results of the 20 year follow-up study published in 1995 regarding

the prevalence of thyroid nodules is of limited value because the study was not designed to assess nodular thyroid disease. The original Whickham study published in 1977 contained one brief statement that thyroid nodules were detected in 5.3% of women and 0.8% of men. However, no details regarding the characterization of nodule size or data regarding thyroid cancer in this cohort were reported (171).

There are no other population-based studies of thyroid nodularity in adults. Ezzat (104) reported results from a small series of adult volunteers who responded to an employee bulletin board and who were given thyroid examinations by two examiners as well as ultrasound and laboratory evaluations. Of the 100 people participating, 21 (21%) had palpable nodules which were confirmed by ultrasound. The high prevalence is likely influenced by the predominance of females (84%), and perhaps the wide age range of 25-77 years.

The use of ultrasonography has greatly increased the sensitivity of detecting anatomical abnormalities or variations of normal in the human thyroid. This technology has raised an important question of whether the high frequency of thyroid UDAs in the general population constitute clinical disease or whether many of these abnormalities represent variations in anatomy that do not adversely affect health. Section X.E.6 below considers the prevalence of thyroid UDAs.

Estimates of the prevalence of thyroid nodules have also been reported based on autopsy findings. One of the most quoted studies of thyroid nodules detected in people dying of non-thyroid disease was published in 1955 by Mortenson (112). These authors performed 821 consecutive autopsies (age range 0-99) and found a prevalence of thyroid nodules to be 49.5%. An older study (173) in 1938 (age range 0-89) found a prevalence of only 8.2% but limited their findings to nodules greater than 2 cm. In 1965 Oertel reported a thyroid nodule prevalence of 13% in previously healthy military men dying from non-thyroid causes (n=113) (174). Other studies by Rice and Hull have found an even higher prevalence of nodules at autopsy (57% and 65% respectively), but were conducted in endemic goiter areas which might explain the high rates of nodularity (175,176).

In summary, the prevalence of thyroid nodules identified in the HTDS cohort (7.2% overall; 9.7% in females and 4.7% in males) is similar in magnitude to that found in the two population-based studies reported in the literature. The slightly lower prevalence in the Framingham cohort most likely reflects a considerably shorter period of follow-up, younger age range, and the absence of the ultrasound screening effect demonstrated for benign nodules in the HTDS. The latter effect of excluding ultrasound has been demonstrated in the HTDS cohort: the cumulative incidence of benign nodules by palpation only (not influenced by ultrasound) is 4.8% for females and 2.0% for males. This value is in quite good agreement with the Framingham prevalence figures. Estimates of prevalence of thyroid nodules based solely on ultrasound detection, or autopsy findings, are considerably higher than in the HTDS cohort and should probably be regarded as an indication of the upper bound of possible prevalence in human populations.

E.3. Prevalence of Hypothyroidism

Hypothyroidism is generally classified into two categories based on severity. Overt hypothyroidism usually produces symptoms and is diagnosed by both elevated TSH levels and decreased levels of circulating thyroid hormone. Subclinical hypothyroidism may or may not produce overt symptoms. It is generally agreed that subclinical hypothyroidism is present when the TSH is between 5 and 10 μIU/ml and thyroid hormone levels are normal. The degree to which subclinical hypothyroidism is included in prevalence studies of hypothyroidism can greatly influence the magnitude of the estimates. In addition, age, gender, and the presence of iodine deficiency or autoimmune thyroid disease also influence the magnitude of the prevalence estimates.

Perhaps the most thorough evaluation of the prevalence of hypothyroidism in an unselected population is the Whickham study and its 20-year follow-up study (171,172). In a review by Wang and Crapo, they indicate it is “the only study that has surveyed a representative sample of the entire adult population of a large community for thyroid disease by employing detailed medical histories, rigorous physical examination, and sophisticated laboratory testing” (167).

The Whickham survey sample was randomly selected from an electoral register of adults older than 18 years in Great Britain. Of the initial sample of 3538 people, 2779 people participated in the study, 1285 men and 1494 women. The age, sex, and social class of the sample generally reflected that of Great Britain. In addition to detailed history and physical examination, each participant was tested for TSH by RIA, free thyroxine index, antithyroid thyroglobulin antibody, and AMA (antithyroid microsomal antibodies). The prevalence of subclinical hypothyroidism (TSH>6 μIU/ml) was 7.5% in women and 2.8% in men (combined, 5.3%). The TSH levels increased with age in women but not in men. The increase with age in women was also seen primarily in those women with positive antithyroid antibodies.

One of the important aspects of the Whickham cohort is that it was followed for 20 years to evaluate the natural history of thyroid disease. Some type of follow-up information was available in over 95% of the original cohort. The results showed that, after a median follow-up of 19 years, the prevalence of hypothyroidism increased significantly. This was in contrast to hyperthyroidism, which remained almost unchanged. The prevalence of spontaneous hypothyroidism in the cohort at the end of follow-up was 4.7% (7.7% in women and 1.3% in men). The overall median age was 58 (38-93), with a median age of 58 for men and 59 for women. These numbers increased further with older women with a prevalence of 10.4% for women older than 45 and 17.5% for women older than 75.

Sawin and colleagues evaluated the Framingham cohort in 1985 and assessed the frequency of hypothyroidism (177). The age range of this cohort, begun in 1948, was between 60 and 89 years of age. For the total cohort of 2139 people at the end of the 15-year follow-up period, 10.3% had an elevated TSH (13.6% for women, 5.7% of men). Excluding those with subclinical hypothyroidism (TSH 5-10 μIU/ml), those with clearly elevated TSH levels (>10 μIU/ml) included 4.4% of the total cohort (5.8% for women and 2.4% in men). Thus, in an unselected aging population, the total prevalence of hypothyroidism was quite high at over 10%.

More recently (1993), Geul and colleagues conducted a population survey in the Netherlands which corroborates the Whickham results regarding risk factors for progression of hypothyroidism (178). TSH and AMA were measured in 423 randomly selected women from the Netherlands, age 40-60, and were repeated ten years later. The prevalence of hypothyroidism at the end of 10 years in the cohort was 7.3% for women, mean age 65.

Several other studies have investigated thyroid deficiency in population based settings. One recent study (1999) evaluated 1411 people representing the majority of individuals from the population of Pescopagano, an iodine deficient community in southern Italy (179). This cohort represented a relatively young population with only 28% of people older than 46 and 30% younger than age 15. Overt hypothyroidism occurred in only 0.2% whereas subclinical hypothyroidism (TSH > 3.7 μIU/ml) occurred in 3.8%. Although this was reported not to be significantly different from that reported in the Whickham study, it is lower than a number of other reports including Framingham and likely reflects the relatively young age of the cohort and perhaps iodine deficiency in the population.

A population-based survey of Danish centenarians has provided interesting information about the effect of very old age on thyroid dysfunction (180). A total of 140 people older than 100 years agreed to have blood tests taken. The number of people with subclinical hypothyroidism was fairly small at 2.9%. An additional 2.9% reported previous hypothyroid disease. The authors concluded that the level of thyroid dysfunction in people older than 100 years was not significantly increased over older people younger than age 100, and that thyroid function in centenarians was well preserved.

The recently published Colorado Health Study involved screening of thyroid function in over 25,000 people at a Health Fair (181). The mean age of the group screened was 56 years with women representing 56%. An elevated TSH was detected in 2450 people (9.5%). Of this group, 1799 people (7.0%) had subclinical hypothyroidism (TSH between 5.1-10 μIU/ml) and 619 people (2.4%) had a TSH greater than 10 μIU/ml. For the age group 45-54, the prevalence of elevated TSH levels was 5% for males and 9% for females; for the 55-64 age group the prevalence increased to 6% for males and 13% for females and continuing increasing with age to about 21% for women greater than age 74.

Finally, Hollowell and coworkers recently reported the results of a large screening study of thyroid abnormalities in a population sampled to represent the geographic and ethnic distribution of the US population (182). The cohort consisted of 31,000 people age 6 and older. The mean TSH was 1.49 μIU/ml for those above 12 years who did not report thyroid disease or thyroid medication. For the age range 40-49, the percentage of people with TSH above 4.5 μIU/ml was 5.7% for females and 3.7% for males, whereas the frequency of positive TPO antibodies was 17.2% in females and 11.3% in males. For the age range 50-59, TSH was greater than 4.5 μIU/ml in 8.1% of females and 2.4% of males; the prevalence of positive TPO antibodies was 18.2% in females and 10.5% in males. While the prevalence of elevated TSH levels was greater among females than males, this difference was not significant after controlling for TPO antibodies. This result is consistent with the results of the Whickham and Geul studies reported above.

In summary, there is considerable information available in the published literature regarding the prevalence of hypothyroidism (both overt and subclinical) in a number of population-based samples of individuals. Estimates of prevalence from the major studies are in reasonable agreement with each other, and define a range which encompasses the estimates derived in the HTDS (7.8% overall; 11.7% in females and 3.7% in males).

E.4. Prevalence of Autoimmune Thyroiditis

Estimating the prevalence of autoimmune thyroiditis is particularly challenging because the antibody assays for detecting autoimmune thyroiditis have changed over time. These assays have ranged from antithyroglobulin measurement via agglutination techniques to antithyroid antimicrosomal antibodies to current and refined methods for detecting thyroid peroxidase antibodies. The reported prevalence of autoimmune thyroiditis in any given study depends on a number of factors, but especially the type of assay used.

The prevalence of antibody positivity in the general population is generally much higher than the prevalence of clinical disease. Although the ability to detect individuals with positive antithyroid antibodies has greatly enhanced the ability to predict risk for developing hypothyroidism, it is nevertheless difficult to predict which individuals with antibody positivity will develop clinical disease. In part, the probability of developing disease is related to the magnitude of the positive test. Summarized below are results from studies of the prevalence of antibody positivity in the general population, with an emphasis on those studies in the last 10-15 years which have utilized more highly sensitive antibody assays.

The Whickham study (reviewed above) also provides important results regarding autoimmune thyroiditis. At the 20-year follow-up, 19% of the cohort had positive antithyroid antibodies (172). The prevalence in women was 26.4% and in men 8.8%. These antibodies were later reported by the authors to be TPO antibodies (183).

An important study by Spencer and colleagues evaluated antibody positivity in thyroid cancer patients and compared them to a group of 4453 people representing the general population who were undergoing routine multiphasic health examinations (184). The mean age of the healthy participants was 45 with a range of 12-99, and a male to female ratio of 0.69. Antibodies to both thyroid peroxidase (TPO) and thyroglobulin were measured. The prevalence of anti-TPO alone was 4.0%, anti-TG was 3.1%, and both TPO and TG antibodies was 7.0%. The prevalence of having <u>any</u> antibody positivity was 14.1%.

The Pescopagano study (described in section X.E.3 above) also assessed antithyroid antibody positivity. The overall prevalence of people positive for both TPO and TG antibody tests was 12.6% (females 17.3%; males 7.0%). Positive antibody tests showed an age effect with a prevalence of 2.4% in children, increasing to 22% in people aged 46-55. No further increases were seen in older people. Although low titer antibody positivity was quite frequent in this cohort, the authors concluded that the spectrum of thyroid disease was not different from that observed in iodine-sufficient areas.

Five additional studies provide data on the prevalence of anti-thyroid antibodies in a healthy unselected population. The Geul study from the Netherlands (discussed in section X.E.3 above) showed that the progression to hypothyroidism was strongly influenced by the presence of autoimmune thyroiditis (178). In a group of 427 women with mean age of 55 (40-60), AMA (antithyroid microsomal antibodies) were measured at the start of the study. The prevalence of positive AMA was 11%. Prentice measured TPO antibodies in 698 female blood donors from seven towns in Great Britain and reported that 18% were positive. The prevalence rose from 15% in women of age 18-24 to 24% in women of age 55-64 (185). Lazarus found similar results in screening 414 asymptomatic elderly women over age 70. The prevalence of positive TPO antibodies was 15% and anti-thyroglobulin antibodies 13% (186). An even higher frequency of positive TG antibodies was found in a small study of patients with thyroid disease compared to 140 healthy volunteers. The volunteer group consisted of 80 women (median age 50) and 60 men (median age 48) in whom care was taken to exclude the presence of thyroid disease. In this group, 27% had positive TG antibodies (187). This is one of the highest frequencies of positive thyroid antibodies reported in a healthy population, although these results are somewhat limited by a very small number of people screened. Finally, the Danish centenarians (described in section X.E.3 above) were also assessed for antithyroid antibodies (180). They were classified into two groups; dependent or independent based on their need for assistance for daily living activities. Those classified as dependent had higher rates of positivity (TPO 11.1%; TG 14.8%; both 22.2%) than those classified as independent (TPO 6.8%; TG 5.1%; both 8.5%).

In summary, there is also considerable information available regarding the prevalence of positive anti-thyroid antibodies in the general population. Estimates range from 3-27%, but are highly variable and are dependent on a number of factors including age, gender, geographical location, type of antibody assay, and perhaps ethnic background and iodine sufficiency as well. Nevertheless, the cumulative incidence estimates for autoimmune thyroiditis in the HTDS cohort (18.2% overall; 23.1% in females and 13.1% in males) are consistent with these estimates in other populations.

E.5. Prevalence of Hyperparathyroidism

The parathyroid glands, located in the back of the thyroid gland, contribute to the regulation of calcium levels in the body through the production of parathyroid hormone (PTH). The most common parathyroid disorder is hyperparathyroidism, which results in high circulating calcium levels due to high levels of PTH secreted from one or more of the parathyroid glands. This disorder is uncommon in comparison to thyroid disease.

Primary hyperparathyroidism has traditionally been defined as an elevated calcium level in the presence of an elevated PTH level. However, because accurate tests of PTH have only become available in the last 10-15 years, early studies have used variable definitions for the disease. Even with the accurate PTH tests available today, the frequency of hyperparathyroidism found from one study to another depends greatly on the cut-off points used by the investigators. For example, a high normal PTH level in the presence of a high calcium is not truly normal and usually represents primary hyperparathyroidism. However, differences in the actual cut-off used from one study to another will result in variable prevalence rates being reported across populations.

Early studies reported a prevalence of hyperparathyroidism of between 0.29% and 1.03% in Swedish men and women age 50-63 (188), and a prevalence of 1.5% in women older than 60 (189). However, these estimates did not reflect a sample of the general population. The prevalence of hyperparathyroidism in the unexposed control group from the studies of atomic bomb survivors in Japan has been reported to be 0.1% in men and 0.3% in women over age 41 (190).

Lundgren and colleagues evaluated 5202 women attending a population-based mammography screening program in Sweden (191). Several definitions of hyperparathyroidism were employed which varied the cutoff points of calcium and PTH. The prevalence of primary hyperparathyroidism in women age 55-75 was 2.1%. This prevalence exceeded that reported by Christensson, which required indisputable hypercalcemia (greater than 2.78 mmole/L) for the diagnosis of hyperparathyroidism rather than high

normal calcium levels in the presence of an increased PTH. Lundgren concluded that the use of current biochemical criteria results in under-diagnosis of primary hyperparathyroidism.

A recent population-based study by Jorde and colleagues from Norway measured serum calcium in approximately 25,000 people who participated in a broad health survey (192). In people with calcium levels greater than 2.59 mmol/L, PTH was also measured. The prevalence of primary hyperparathyroidism in this group (ages 25-75) was 0.17% for men and 0.45% for women ($p<.001$). A subgroup analysis was performed in older women between ages 50 and 75. Using the criteria for the main study, the prevalence of hyperparathyroidism was 8.8%. However, the prevalence varied dramatically from 3.6% to 13.9% when the criteria for hyperparathyroidism were varied.

Despite the substantial difficulties in comparing prevalence estimates of hyperparathyroidism in different populations due to differences in diagnostic definitions used, the cumulative incidence estimates from the HTDS (0.3% overall; 0.6% in females and 0.1% in males) are well within the range of estimates found in the published literature.

E.6. Prevalence of Thyroid Ultrasound-Detected Abnormalities of the Thyroid (Thyroid UDAs)

During the last 15 years, high-frequency ultrasound has increasingly been used in the evaluation of thyroid nodules. Although the traditional definition of a thyroid "nodule" has been based on clinical palpation, the greater sensitivity of ultrasonography has led to its increased use and consequently the detection of nonpalpable, millimeter-size abnormalities. This has raised several important issues: 1) thyroid UDAs have been shown to occur frequently in the general population, without an adequate understanding of their risk of malignancy or biologic significance; 2) thyroid UDAs have often been classified as "nodules" regardless of size. This has resulted in uncertainty about whether palpable ultrasound-detected nodules are biologically different than the large numbers of nonpalpable ultrasound-detected "nodules"; 3) the use of ultrasound in defining criteria for thyroid nodules has made it difficult to compare clinical thyroid outcomes across epidemiological studies if they use different criteria for thyroid nodularity; and 4) although ultrasound has exceptional sensitivity, recent data regarding specificity (the ability to distinguish benign from malignant nodules) suggests that the increases in specificity of ultrasonography are associated with significant decreases in the sensitivity.

A number of studies have shown that the prevalence of thyroid UDAs is high in the general population. Tan et al. have recently reviewed the literature and reported a range of prevalence of 17-67% (102). In 1000 people evaluated for hypercalcemia, in whom 8% had a nodular goiter, 46% had discrete lesions on ultrasound and 38% were reported to have nodules (103). The study reporting the highest prevalence of thyroid UDAs was a prospective study of 100 employees responding to a notice on a bulletin board: 67% of these women, mean age 43, showed abnormal thyroid ultrasound scans (104). Thyroid UDAs in populations without apparent thyroid disease have also been documented outside the US with prevalence figures ranging 17-27% (105-107). Most of these studies have been consistent in showing that nonpalpable thyroid UDAs are generally small and that solitary nodules on clinical examination are often associated with multiple other thyroid UDAs. Both Tan (102) and Brander (105) have demonstrated that in patients with known palpable thyroid nodules greater than 1 cm, 48% harbored additional thyroid nodules found on ultrasound.

Brander and colleagues have also published a comprehensive study regarding the prevalence of thyroid UDAs. They randomly selected 253 people from a Finnish city council registry and screened for thyroid UDAs (109). The sample was distributed evenly among four age brackets from 20 through 50. The community was not thought to be endemic for goiter. Thyroid UDAs were detected in 69 people (27.3%). These abnormalities were solitary in 57%, multiple in 22%, and diffuse in 22%. The mean age for people with normal ultrasound scans was 35, the mean age for the group with abnormal ultrasound findings was 37. These abnormalities were found more often in women than men and increased with age for both sexes. For women, the prevalence of thyroid UDAs was 30% in the 20-29 age group, 32% in the 30-39 age

group, and 41% in the 40-50 age group. All participants underwent thyroid palpation prior to ultrasound examination. Palpable abnormalities were detected in 13 people (5.1%); three with a solitary nodule, five with multiple nodules, and five with abnormal consistency. Fine needle aspirations were done in 30 individuals. All were negative for malignancy with one intermediate probably of neoplasm; that person underwent surgery and had a follicular adenoma.

Bruneton evaluated 1000 healthy volunteers without history of thyroid disease and performed high frequency thyroid ultrasound examinations (111). Although selection criteria or mean age were not provided, 57% of participants were over 50 years. Ultrasonography was performed with 13 MHz transducers and all ultrasound nodules greater or equal to 3 mm were counted. One or more nodules were detected in 34.7% of subjects. For people less than age 50 (n=431), the prevalence was 25%. For people greater than age 50 (n=569), prevalence was 42%. For all ages, the prevalence in women was 44% and the prevalence in men was 17.7%.

A Belgian study assessed thyroid ultrasound abnormalities in 300 patients who were referred for abdominal ultrasound examinations (107). Although this study sample is not a random representation of the general population, there were extensive exclusion criteria for those with symptoms or signs of thyroid disease. Unlike the Bruneton study, this investigation used a 5.5 MHz ultrasound transducer. The mean age was 47 (range 1-88 years) and 55% of the participants were males. Small echoic nodules were found in 19% of patients. In patients in their seventh decade of life, the prevalence increased to over 40%. The wide age distribution of this cohort and the high percentage of males undoubtedly influenced these results.

In summary, there is considerable published evidence reporting high prevalence of thyroid abnormalities detected by ultrasound examination in the general population. Estimates of 40%-50% or even greater are not uncommon, depending upon the characteristics of the population screened and the technology used. The prevalence of any UDA found in the HTDS (46.5% overall; 55.5% in females and 37.4% in males) are consistent with these estimates.

In overall summary, a considerable effort was made to assess the world literature on the prevalence of the major thyroid and parathyroid disease outcomes evaluated in the HTDS as well as thyroid UDAs. This was done in order to compare the disease experience of the HTDS cohort to what might reasonably be expected based on the experience in other populations not exposed to Hanford radiation. As outlined at the beginning of this section, comparisons of this type are imperfect and must be interpreted with great caution. What appear to be differences in prevalence estimates between the HTDS cohort and other populations may well reflect differences in any of a number of factors other than exposure to radiation from Hanford. Nevertheless, it is clear from comparisons with the most comparable studies in other locations that for the major outcomes described above (thyroid nodules, thyroid cancer, hypothyroidism, autoimmune thyroiditis, hyperparathyroidism, and thyroid UDAs), the estimates of cumulative incidence or prevalence derived from the HTDS are well within the range and are consistent with published estimates. There is no indication that the levels of disease occurrence in the HTDS cohort are systematically different, or higher, than what has been reported around the world in a variety of different circumstances.

F. Summary and Conclusions

The HTDS was conducted to determine whether exposure to atmospheric releases of primarily ^{131}I from the Hanford Nuclear Site between 1944 and 1957 resulted in increased thyroid disease among those exposed. The study evaluated twelve categories of thyroid disease, the results of several laboratory tests for thyroid function, anti-thyroid antibody and serum calcium level, thyroid UDAs, thyroid mass, and hyperparathyroidism. The primary analysis utilized an estimate of thyroid radiation dose for each individual based on information about their residence history and dietary consumption patterns during the times of the Hanford releases. Additional analyses were also conducted using several alternative methods for estimating dose, both quantitative and qualitative, including methods which were independent of the HEDR models. The primary analyses were based on a sex-stratified linear dose-response model, although alternative models for the shape of the dose-response were also investigated. The potential effect on any

dose-response of a number of lifestyle factors and indicators of other radiation exposure were evaluated as covariates in the models. All primary dose-response analyses were repeated to include adjustments for uncertainty in the individual radiation dose estimates.

This study found no statistically significant association between dose to the thyroid from Hanford radiation and 1) cumulative incidence of any of the disease outcomes; 2) prevalence of thyroid UDAs; or 3) thyroid laboratory tests or thyroid mass. There was also no evidence of a dose-response for hyperparathyroidism, although a positive dose-response was seen for serum calcium. An increasing thyroid dose was significantly associated with a decrease in serum calcium. Although the explanation for this result is not clearly apparent, the finding does not appear to be of clinical significance (discussed more fully in section IX.Q.7 above). These results remained the same when alternative methods of assessing radiation dose were used, and after accounting for uncertainty in dose estimation. Based on data available regarding the tracing and enrollment of study participants, there is no evidence that the absence of a dose-response relationship is due to bias in selection of the cohort, loss to follow-up, or enrollment and participation.

Given the principal differences between the radiation exposure circumstances at Hanford and those of other populations studied in relation to radiation-induced thyroid disease (summarized above), the findings of this study are not inconsistent with the current published literature regarding the effect of exposure to radioactive iodine and the risk of thyroid and parathyroid disease. This is particularly so given the relatively small magnitude of the estimated thyroid radiation doses in members of the HTDS cohort (mean = 174 mGy) and the relatively protracted nature of the exposure over time. There is little evidence in the literature to suggest that people exposed to ^{131}I at the levels found in this study over a period of months or years would experience higher rates of thyroid or parathyroid disease as a result of their exposure.

Nevertheless, a lingering question for many may be whether the uncertain nature of the dose estimation used in the primary analyses is so great that it renders the quantitative dose-response results inconclusive. The study has attempted to address this possibility in three ways. First, alternative qualitative methods of assigning exposure were used. Results from these analyses were consistent with those from the quantitative dose-response analyses. Second, two different approaches were employed to evaluate the impact of dose uncertainty on the primary risk estimates. Neither resulted in findings that were materially different from those ignoring such uncertainty. Third, the impact of dose uncertainty on study power was assessed using simulation methods. These analyses revealed that the reduction in statistical power due to uncertainty in dose estimation was modest, and that even after accounting for such uncertainty the study had adequate statistical power to detect effects as small or smaller than those in the existing published literature. Although any epidemiologic study is limited to some extent by uncertainty in the assessment of exposure, the impact of such uncertainty on the power of the study and the estimation of risk is seldom addressed to the extent attempted here. Further, the fact that epidemiologic investigations are inherently "uncertain" does not imply complete randomness or unpredictability, nor does it mean that reasonable conclusions cannot be drawn from such studies.

In conclusion, the results of the HTDS provide no evidence of a statistically significant association between increasing thyroid radiation dose from Hanford and the cumulative incidence of any of the disease outcomes studied or the prevalence of thyroid UDAs. These findings do not definitively rule out the possibility that Hanford radiation exposures are associated with an increase in one or more of the outcomes under investigation. However, it does mean that if such associations exist, they were likely too small to detect using the best epidemiologic methods available.

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Hanford Thyroid Disease Study
Pilot Study Report: Executive Summary

EXECUTIVE SUMMARY

The Hanford Thyroid Disease Study (HTDS) was mandated by an act of Congress in 1988. The Centers For Disease Control and Prevention (CDC) was directed by Senate Bill 2889 to conduct a study of thyroid morbidity among persons who lived near the Hanford Nuclear Site between 1944 and 1957. A team of investigators at the Fred Hutchinson Cancer Research Center (FHCRC) and the University of Washington in Seattle was selected by the CDC to conduct the study, and a contract was awarded to the FHCRC on September 19, 1989.

The primary purpose of the study is to determine whether thyroid morbidity (including, but not limited to hypothyroidism, benign neoplasia, and malignant neoplasia) is increased among persons exposed to releases of radioactive iodine from the Hanford Nuclear Site between 1944 and 1957, and who received radiation doses to the thyroid as a result, relative to persons who received a very low or negligible radiation dose to the thyroid from Hanford. If an effect is detected, the study is designed to further determine in what way the increase in thyroid morbidity is related to the dose of radiation received (i.e., the characteristics of any dose-response relationship).

This study is being conducted as a follow-up prevalence study. That is, subjects are selected on the basis of presumed past exposure to radioactive iodines from Hanford, based on place and year of birth, are located, and are examined for the presence or history of thyroid disease. The primary analyses will focus on living participants who receive medical examinations to detect thyroid disease, and for whom thyroid radiation doses are estimated using the dosimetry system developed by the Hanford Environmental Dose Reconstruction (HEDR) Project. Deceased subjects and others for whom less complete information is available will be included in secondary analyses. Although the effects of primary interest are defined by three categories of thyroid disease (hypothyroidism, benign thyroid nodules, and thyroid cancer), information regarding all forms of thyroid disease is being recorded as part of the study and will be included in the overall analysis. In addition, hyperparathyroidism is being evaluated by screening individuals for hypercalcemia.

The work is being conducted in two stages. The first is a Pilot Study, the primary purpose of which is to evaluate the feasibility of the methods proposed, and to develop the specific operational procedures and data collection instruments needed for a full study. If the results of the Pilot Study indicate that it is feasible to conduct a successful full-scale epidemiologic study, the second stage will be to implement the remaining field work to complete such a study. This approach allows the accumulation of information and experience prior to initiation of a more costly full-scale study. Based on the experience gained in the Pilot Study, the design and procedures for a full study can be modified if necessary to account for the realities of the field environment.

As of this writing the pilot phase of the HTDS is essentially complete. The large majority of Pilot Study participants completed the clinical examination portion of the study by the end of December, 1994. Thus, there are now sufficient data available from the Pilot Study to adequately evaluate the specific objectives of this initial phase of the project. This report describes the primary findings from the Pilot Study.

Locating Study Subjects and Recruiting Them To Participate in the Study

The Pilot Study has demonstrated that it is feasible to locate persons using birth certificate records from the early to mid-1940s. Overall, 91% of the 1590 Pilot Study subjects identified from birth certificates have been located. Success in locating people has not differed substantially according to sex, year of birth, or geographic area of birth. The majority of Pilot Study participants subjects have been found to still reside in Washington state, and approximately three quarters live in the Pacific Northwest. The Pilot Study has also demonstrated that once located, and contacted by phone, a large proportion of individuals (85%) will agree to participate in the study. Willingness to participate does not differ substantially according to the region in which the person was born, nor according to sex or year of birth. These results indicate that the methods developed for identifying a cohort, locating individual members of the cohort, and recruiting them to participate in the study are feasible and are likely to result in relatively high levels of success.

Obtaining Information and Biological Specimens From Study Participants and Families

The Pilot Study has demonstrated that: 1) for approximately 75% of the study participants, a respondent can be identified who is willing to be interviewed by telephone regarding the participant's childhood and adolescence (to provide detailed information used to estimate a thyroid radiation dose); 2) that the participant's birth mother can serve as the telephone interview respondent in about 75% of the cases in which a respondent is identified; 3) that other immediate family members can be located and will agree to participate in most of the remaining cases; 4) that it is feasible to complete the telephone dosimetry interview for virtually all of those who agree to participate; and 5) that it is feasible to administer an expanded version of the In-Person Interview to study participants for whom a telephone respondent cannot be recruited.

Furthermore, the Pilot Study has demonstrated that it is feasible to schedule and conduct clinics in a manner that will include those identified and willing to participate, that participants will agree to participate in all components of the clinical phase of the study, including fine needle aspiration if recommended, and that participants will provide written consent to obtain prior medical records relevant to thyroid disease. It is still too early to adequately assess the success with which medical records can be obtained. Preliminary indications are that it will be possible to obtain more than 60% of the records requested.

Adequacy of Study Procedures, Forms, and Data Collection Instruments

The Pilot Study has been an on-going test of study procedures, forms, and data collection instruments. All study procedures are documented in a Procedures Manual, which is updated as changes are implemented. The operational procedures and associated forms and instruments currently in place are working well. Changes are made when specific circumstances arise that can best be addressed by instituting a procedural change. An internal Problems Form is used extensively by study staff to document problems, solutions, and any procedural changes that result. Changes will continue to be made on a continuing basis as the need arises.

Estimation of Radiation Dose Distributions and Power and Sample Size Calculations

Thus far, thyroid radiation doses have been calculated for 869 Pilot Study participants using the dosimetry system developed by the HEDR Project. The information about an individual participant's dose is actually provided as a set of 100 dose estimates, each corresponding to one realization of the integrated simulations produced by the HEDRIC computer programs. Dose distributions for the 869 Pilot Study participants are provided in this report according to year of birth (1942-1946), gender, and geographical region of birth (eight areas surrounding the Hanford Site). These results have suggested that in order to identify persons with the highest doses, further selection from the strata defined for the Pilot Study should be limited to the years 1942-1944 and to the Richland, Pasco/Kennewick, Benton County, and Franklin County strata.

Utilizing projections based on the Pilot Study dose distributions, power calculations were conducted for tests of the dose response for the endpoints thyroid neoplasia, thyroid malignancy, and ultrasound-detected abnormality. Three plans are presented for selecting potential study participants to complete a full study. Projected power functions of tests for radiation dose response functions based on these plans are presented for the three classes of endpoints listed above. The results of these calculations suggest: 1) that cohorts identified from birth records are likely to provide a sufficiently wide distribution of doses for successful completion of a full study; and 2) that the cohorts defined for the Pilot Study are likely to be inadequate to complete a full study, and that they should be augmented by the additions of 1940-41 births in Benton and Franklin Counties, and 1940-1944 births in Adams County. Such a sampling plan will, under a plausible but conservative projection, provide reasonable statistical power (>0.80) to detect an increase in the risk of thyroid neoplasia of 5.5% per Gy.

Plan For Conducting A Full Study

Based on the results available to date from the Pilot Study regarding logistical success, thyroid dose distributions, and numbers of births in the Hanford region during the early to mid-1940s, a plan was developed for completing a full epidemiologic study. The plan is based upon a number of important assumptions: 1) the thyroid dose distributions obtained thus far in the Pilot Study are reasonably representative of what will be the overall dose distribution at the

completion of a full study; 2) approximately 3200 living evaluable subjects will be required to achieve the level of power referenced above; 3) the basic study design and data collection methods will remain the same; 4) if continued, the ultrasound follow-up component of the study will be staffed and conducted separately from the main study clinic; 5) the dose calculations for study participants will be conducted by HTDS staff through remote access to the HEDR computer programs at the CDC in Atlanta; and 6) the study will be completed near the end of 1997.

The following are the key elements of a plan designed to achieve the goal of completing the study near the end of 1997 with at least 3200 living individuals evaluated.

1. Add to the sample all births from the following areas and years
    a. 1942-1944: remaining Richland, Pasco\Kennewick, and Benton County
    b. 1940-1941: all of Benton and Franklin Counties
    c. 1940-1944: all of Adams County
2. Focus on completing the tracing of study subjects quickly

    a. Hire additional staff in early Fall of 1994
    b. Complete a substantial proportion of the tracing by early 1995
    c. Complete the large majority of tracing by mid-1995
    d. Complete all tracing by mid-1996

3. Increase staff support in several areas

    a. Administration (travel, office)
    b. Recruiting and scheduling
    c. CATI interviewing (two interviewers)
    d. Clinics (one phlebotomist, one interviewer)
    e. Statistics

4. Expand clinic operations

    a. Increase the number of clinic days held per month to 6-7
    b. Increase the number of study participants at clinics to 100-120/month
    c. Conduct ultrasound follow-up clinics separately from the main clinics

In order to achieve the plan summarized above, the identification and selection of additional study subjects and accelerated tracing efforts have already begun in anticipation of conducting a full study. Tracing efforts will be conducted up to but not including the point of recruiting individuals into the study, pending final approval of this plan by the CDC. A preliminary version of this report was submitted to the National Research Council's Board of Radiation Effects Research of the Commission on Life Sciences on August 25, 1994. A report was issued from the Board on November 16, 1994 which stated, "On the basis of the written report and the presentations and in light of the unique experiences of the population around Hanford, the quality of the information obtained in the Hanford Thyroid Disease Study, and the effort expended in the Hanford Environmental Dose Reconstruction Project, the committee unanimously recommends the continuation of the Hanford Thyroid Disease Study." The Board's report and this final report will be submitted to the HTDS Federal Advisory Committee at a meeting on February 22, 1995, at which time a recommendation from the Advisory Committee regarding the continuation of the study will be made. Shortly thereafter it is anticipated that a final decision will be made by the CDC regarding the full study.

If a full study is approved, expanded operations would begin in March or April of 1995. It is expected that such a timeline would allow for the completion of the study near the end of 1997.

sums as may be necessary for fiscal year 1990.''; and

(2) in paragraph (3), by inserting after "made available" the first place It appears the following "to the Secretary, acting through the Administrator of the Health Resources and Services Administration.".

Subtitle L-Fetal Research *Moratorium*

SEC. 156. EXTENSION OF MORATORIUM.

Section U.S.C. 289g(c)) is amended-

(1) in paragraph (2), by striking "thirty. six month period beginning on the date of enactment of this section" and inserting "24-month period beginning on the date of the enactment *of* the National Institute on Deafness and Other Communication Disorders and Health Research Extension Act of 1988"; and

(2) in paragraph (3), by striking "1988" and inserting "1990".

SEC. 157. BOARD AND STUDY.

(a) AUTHORIZATION

Section 381(e) (42 U.S.C. 275(e)) is amended by striking "and" after "1987." and inserting before the period the following: ", $2,000,000 for fiscal year 1989. and $2.500.000 for fiscal year 1990".

(b) STUDY.—Section 498(c)(1) (42 U.S.C. 289g(c)(1)) is amended by striking "thirty months after the date of enactment of this section" and inserting "24 months after the date of the enactment of the National Institute on Deafness and Other Communication Disorders and Health Research Extension Act of 1988".

Subtitle M—Miscellaneous

SEC. 161. STUDY OF THYROID MORBIDITY FOR HANFORD, WASHINGTON.

(a) IN GENERAL.—In carrying out the purposes of section 301 of the Public Health Service Act (42 U.S.C. 241), the Secretary of Health and Human Services, acting through the Director of the Centers for Disease Control (hereafter referred to in this section as the "Director'?. shall conduct a study of thyroid morbidity of the population tincluding Indian tribes and tribal organizations) in the vicinity of Hanford. in the State of Washington during the years 1944 through 1957.

(b) PEER REVIEW.—As soon as is practicable after the date of the enactment of this Act. the Director shall establish a peer review committee that shall. along with the Centers for Disease Control. make any determinations as to the conduct of the study required under this section.

(c) CONTRACTS.—

(1) ENERAL.—Except as provided ln paragraph (2), the Director may contract out any portion of the study required under this section if the Director considers such appropriate. except that such contractor shall not have any direct or indirect interest in the outcome of such study including, contracts with the Department of Energy.

(2) RELATIONSHIPS.—Contractors that currently are parties to contracts with the Department of who have previously been parties to such) shall be given consideration pursuant to paragraph (1), except that the Director shall make a determination in each such circumstance that the relationship of the contractor with the Department of Energy does not represent a conflict of interest or the appearance of such a conflict regarding the conduct of the study required under this section.

(d) REPORT.—Not later than 42 months after the date of enactment of this section. the Director shall transmit a report including such study to the Congress. the chief executive officers of the States of Oregon and Washington. and the governing officials of the Indian tribes in the vicinity of Hanford, Washington.

SEC 162. ON SLEEP DISORDERSRESWRCH.

(a) ESTABLISHMENT.—Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (hereafter in this section referred to as the "Secretary"), after consultation with the Director of the National Institutes of Health. shall establish a National Commission on Sleep Disorders Research (hereafter in this section referred to as the "Commission").

(b) COMPOSITION.—

(1) APPOINTED MEMBERS.—The Commission shall be composed of 10 members to be appointed as follows:

(A) Six members shall be appointed by the Secretary from among scientists, physicians, and other health professionals who are not in the employment of the Federal Government. and who have primary expertise in sleep disorders research or medicine.

(B) Two members shall be appointed by the Secretary from the general public, of whom one of which shall have personal or close family experience with sleep disorders.

(C) Two members shall be appointed by the Secretary from among the personnel of the National Institutes of Health, and such members interest shall be in the field of sleep disorders research.

(2) Ex OFFICIO MEMBERS.—The Director of the National Institutes of Health, the Director of the National Institute of Neurological and Communicative Disorders and Stroke, the Directors of the National Heart, Lung and Blood Institute, the National Institute on Mental Health, the National Institute on Aging, the National Institute on Chlld Health and Human Development, the Director of the Center for Disease Control. the Chief Medical Director of the Veterans. Administration, and the Secretary of Defense shall be ex officio members of the Commission. or their designees.

(c) CHAIRPERSON.—The members of the Commission shall select a Chairperson from among the appointed members of the Commission.

later than 60 days after the establishment of the Commission, the Commission shall meet as directed by the Secretary, and thereafter shall meet at the call *of the* Chairperson of the Commission. but in no event shall the Commission meet less often than three times during the life of the Commission. The Commission may hold such hearings, take such testimony, and sit and act at such time and places as the Commission considers appropriate.

(e) PERSONNEL.—

(1) EXECUTIVE SECRETARY.—

(A) APPOINTMENT.—The Commission may appoint and flx the compensation of an executive secretary to effectively carry out the functions of the Commission.

executive secretary shall be appointed subject to title 5, United States Code, governing appointments in the competitive service, and shall receive compensation in accordance with chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates.

(2) ADDITIONAL PERSONNEL.—The Secretary shall, to the extent practicable, provide the Commission with such additional professional and clerical staff. such information. and the services of such consultants as the Commission determines to be necessary to carry out its functions effectively.

(f) COMPENSATION.—

(1) OFFICERS OR EMPLOYEES OF THE FEDERAL GOVERNMENT.—Members of the Commission who are officers or employees of the Federal Government shall serve as members of the Commission without compensation in addition to that received in their regular public employment.

(2) NON-FEDERAL GOVERNMENT MEMBERS.—Members of the Commission who are not officers or employees of the Federal Government shall receive compensation at a rate not to exceed the dally equivalent of the annual rate in effect for Grade GS-18 of the General Schedule for each day tincluding traveltime) that such members are engaged in the performance of their duties as members of the Commission.

(3) EXPENSES.—All members of the Commission, while serving away from their homes or regular places of business in the performance of services for the Commission. shall be allowed travel expenses. including per diem in lieu of subsistence, in the same manner as such expenses are authorized by section 5703 of title 5. United States Code. for persons in Government Service employed intermittently.

(g) DUTIES.—

(1) STUDY.—The Commission shall-

(A) conduct a comprehensive study of the Present state Of knowledge of the incidence. prevalence. morbidity, and mortality resulting from sleep disorders. and of the social and economic impact of such disorders;

(B) evaluate the public and private facilities and resources (including trained personnel and research activities) availableforthe diagnosis, prevention. and treatment of, and research into. such disorders: and

(C) identify programs (including biological, physiological, behavioral. environmental. and social programs) by which improvement in the management and research into sleep disorders can be accomplished.

(2) DEVELOPMENT OF PLAN.—Based on the study conducted under paragraph (1), the Commission shall develop a long-range plan for the use and organization of national resources to effectively deal with sleep disorders research and medicine.

(3) COOPERATION.—Each Federal entity administering programs and activities related to sleep disorders shall. *on* request, *assist* the Commission in carrying out its duties under this subsection.

(h) DEVELOPMENT or ESTIMATES.—The Commission shall recommend for each of the Institutes of the National Institutes of Health whose activities are to be affected by the long-range plan. estimates of the expenditures needed to carry out each Institute's part of the overall program. Such estimates shall be prepared for the fiscal year beginning immediately after completion of the plan under subsection (g)(2) and for each of the next 2 fiscal years.

(i) REPORT.—Not later than 18 months after the initial meeting of the Commission (as prescribed by subsection (d)), the Commission shall prepare and submit to the appropriate Committees of Congress, a final report describing—

(1) the long-range plan developed under subsection (g);

(2) the expendlture estimates required under subsection (h); and

(3) any recommendations of the Commission for legislation.

(j) TERMINATION.—The Commission shall cease to exist on the 30th day following the date of the submission of the final report under subsection (i).

SEC. 163. MISCELLANEOUS AMENDMENTS.

The Public Health Service Act (42 U.S.C. 201 et seq.1 is amended-

(l)(A) with respect to section 303(a), by transferring the matter after and below paragraph (2) of such section to section 301:

(B) by designating such matter as subsection (d); and

(C) by addlng subsection (d) (as so designated) at the end of section 301:

HTDS ACTIVITY/SOURCE RECORD

Subject ID number: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ Birth name: _____ Page _____ of _____

Step	*Date*	*Initial*	*Information source*	*Phone number*	*Outcome*	*Next action*

HTDS TRACING CHECK LIST

HTDS ID number: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Subject's birth name: _____

SOURCES USED FOR THIS SUBJECT

_____ 01) Telephone directory _____
_____ 02) CD-ROM directory _____
_____ 03) City/reverse directory _____
_____ 04) Directory assistance _____
_____ 05) Dept.of lic. match _____
_____ 06) Death cert. match _____
_____ 07) Birth cert. match _____
_____ 08) LDS genealogy recs. _____
_____ 09) Marriage records _____
_____ 10) Tax assessor's recs _____
_____ 11) Voter registration _____
_____ 12) Military records _____
_____ 13) Employment records _____
_____ 14) High Sch. reunion _____
_____ 15) Sch registration recs _____
_____ 16) Former sch. teachers _____
_____ 17) Obituaries _____
_____ 18) Postal Service _____
_____ 19) Utility records _____
_____ 20) Locating services _____
_____ 21) Relative _____
_____ 22) Neighborhood search _____
_____ 23) Veteran's orgs _____
_____ 24) Agricultural orgs _____
_____ 25) Civic organizations _____
_____ 26) Religious orgs _____
_____ 27) Labor unions _____

_____ Other, specify: _____

_____

_____

_____

_____

Date sent to Seattle: _____ _____ / _____ _____ / _____ _____
Month Day Year

HTDS WEEKLY TRACING SUMMARY

HTDS ID number: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Subject's birth name: _____

Week ending: _____ _____ / _____ _____ / _____ _____
Month Day Year

***NEW* SOURCES USED THIS WEEK**

Check all NEW sources that apply

_____ 01) Telephone directory
_____ 02) CD-ROM directory
_____ 03) City/reverse directory
_____ 04) Directory assistance
_____ 05) Dept.of licensing match
_____ 06) Death certificate match
_____ 07) Birth certificate match
_____ 08) LDS genealogy records
_____ 09) Marriage records
_____ 10) Tax assessor's records
_____ 11) Voter registration
_____ 12) Military records
_____ 13) Employment records
_____ 14) High School reunion lists
_____ 15) School registration records
_____ 16) Former school teachers
_____ 17) Obituaries/Funeral Homes
_____ 18) Postal Service
_____ 19) Utility records
_____ 20) Locating services
_____ 21) Relative
_____ 22) Neighborhood searches
_____ 23) Veteran's organizations
_____ 24) Agricultural organizations
_____ 25) Civic organizations
_____ 26) Religious organizations
_____ 27) Labor unions
_____ 28) Sibling match (other subjects)
_____ 29) Death index/death records
_____ 30) Response to ID letter
_____ 31) Online services (e.g., DCS)
_____ 32) Credit bureaus

_____ Other, specify: _____

_____

TASKS PERFORMED THIS WEEK FOR THIS SUBJECT

Check all tasks that apply

_____ 01) Made telephone calls
_____ 02) Travelled out of office
_____ 03) Reviewed list of matches
_____ 04) Searched various directories
_____ 05) Searched other sources
_____ 06) Set up files
_____ 07) ID letter sent

_____ 98) Other, specify:_____

_____

_____

Status of subject at end of this week (check ONE):

_____ 01) Subject not yet located

_____ 02) Subject located, confirmed by direct contact with subject
_____ 03) Subject located, confirmed by contact with someone other than subject
_____ 04) Subject located, NOT confirmed by contact

_____ 05) Subject DECEASED, surrogate not yet located
_____ 06) Subject INCAPACITATED, surrogate not yet located

_____ 07) Surrogate located, confirmed by contact
_____ 08) Surrogate located, NOT confirmed by contact

_____ 09) Subject ineligible, specify reason:
_____

_____ 98) Other, specify: _____

Overall prospect for locating subject (check ONE):

_____ 1) Subject located
_____ 2) Too early to tell
_____ 3) Excellent (definite, will probably locate within the next month)
_____ 4) Good (likely)
_____ 5) Not good (unlikely, but possible)
_____ 6) No way

REQUEST FOR ACTION:

_____
_____
_____
_____

Data collection specialist's initials: _____ _____

For Seattle use only:

Data entry specialist's initials: _____ _____
Date of key entry: _____ _____ / _____ _____ / _____ _____
Month Day Year

CATI RESPONDENT INFORMATION AND ASSESSMENT

Respondent Relationship: _____

RESPONDENT NAME: _____

STREET ADDRESS: _____

CITY/STATE/ZIP: _____

PHONE: ( ) _____

SUBJECT NAME: _____

ASSESSMENT:		
1.	**Does (respondent) live independently?** ____ YES ____ NO	***If NO, explain:***
IF NO:	**Would a phone be available for a 1 to 2 hour phone call?** ____ YES ____ NO	
2.	**Does (respondent) have a hearing impairment?** ____ YES ____ NO	***If YES, explain:***
IF YES:	**Is (respondent) able to hear well over the phone?** ____ YES ____ NO	
3.	**Would (respondent) be able to read materials we send?** ____ YES ____ NO	***If NO, explain:***
IF NO:	**Is there assistance available for written materials?** ____ YES ____ NO	
4.	**Does (respondent) have any health problems or impairments that would make it difficult to be interviewed over the phone for 1 to 2 hours? (e.g., arthritis, back trouble, stroke, speech problems)** ____ YES ____ NO	***, If YES, explain:***

OTHER CONSIDERATIONS:	
GOOD TIMES TO CALL:	***BAD TIMES TO CALL:***
GENERAL COMMENTS:	

RECRUITER: _____ DATE: ____ / ____ / ____

INTERVIEWER: _____

REFUSAL QUESTIONNAIRE

HANFORD THYROID DISEASE STUDY

September 29, 1992

PHASE INITIALS DATE	
EDITED	SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __ __
CODED	INTERVIEWER ID: ___ ___
KEYED	DATE OF INTERVIEW __ __ / __ __ / __ __
VERIFIED	

Even though you are declining participation in this study, there are 12 short questions I would like to ask so that we will have a little information about all the people who were selected. This shouldn't take more than five minutes of your time. Would you be willing to answer these questions now?

If no: Thank you for your time. ***End contact.***

If yes, proceed:

Before we begin, there are a few things I need to mention:

* All of the information you provide will be kept strictly confidential as required by public law PHS Act Section 308(d)(42 USC 242m(d)).
* If you choose not to answer one of the questions, simply tell me and we will move on to the next question.
* You may end this interview at any time.

1. ***(If you have some general information about reason for refusal already, say:*** I know you've already told me, but just so I get it right...***)*** Could you tell me why you have chosen not to participate in this study? ***Record answer. Clarify any concerns; address any questions. If turn-around opportunity arises, proceed from the point participation initially broke off.***

Although you are not interested in participating in this study, it would still be helpful to us to know something about people who decline participation.

2. What race or ethnic origin do you consider yourself to be? ***LIST 1-6***

White/Caucasian	01	QX 6
Black/Negro	02	QX 6
Asian or Pacific Islander	03	QX 6
Native American (American Indian or Alaskan Native; Aleut or Eskimo)	04	
Spanish or Hispanic	05	QX 7
Other race (*Specify*: _____)	06	QX 6
Don't Know	09	QX 6
Refused	77	QX 6

3. What is your Native American ancestry? ***Record answer***

4. Are you an enrolled member of a Federally recognized Tribe or Nation?

Yes	01	
No	02	QX 6
Don't Know	09	QX 6
Refused	77	QX 6

5. Which Tribe or Nation? ***Record answer***

6. Are you of Spanish or Hispanic Origin?

Yes	01	
No	02	QX 8
Don't Know	09	QX 8
Refused	77	QX 8

7. What is your Hispanic origin? ***List 3-7***

Cuban	03
Mexican	04
Puerto Rican	05
Spanish	06
Other (specify: _____)	07
Don't Know	09
Refused	77

8. What is your religious preference? ***READ LIST***

Protestant 01
Catholic 02
Jewish.....03
Mormon 04
Seventh Day Adventist 05
Other (*Specify*: _____) 06
None.....07
Refused 77
DK.....99

9. What is your marital status? ***READ LIST***

Married or living as married 01
Widowed.....02
Divorced.....03
Separated.....04
Never Married.....05
Refused 77

10. What is the highest grade or level you attended in school? ***READ LIST, if necessary***

Grade School, up to grade 8.....01
Some High School, grades 9-12.....02
High School graduate or GED 03
Graduate of Technical School or 2-year College.....04
Some college.....05
College graduate 06
Graduate School.....07
Other (*Specify*: _____) 08
Refused 77

11. Last year at this time, how many people were living in your household?

Record answer: ____ ____

12. In (ONE YEAR BEFORE INTERVIEW DATE), what was your combined household yearly income before taxes? ***READ 1-4***

Less than $15,000 a year.....01
$15,000 to $30,000 a year.....02
$30,000 to $45,000 a year.....03
More than $45,000 a year 04
Refused 77
DK.....99

Thank you for taking the time to answer these questions.
If you later reconsider and would like to participate in this study, please contact our office.

REFUSAL TO PARTICIPATE ASSESSMENT: SUBJECT

HANFORD THYROID DISEASE STUDY

March 3, 1995

	INITIALS	DATE	
			SUBJECT ID #: _____
CODED	_____	_____	
			COMPLETED BY: _____
KEYED	_____	_____	
			DATE OF REFUSAL __ __ / __ __ / __ __
VERIFIED	_____	_____	

Refusal to participate = the potential participant does not agree to participate in the study

1. Type of refusal?

   Refusal to participate on 1st Attempt 01
   Refusal to participate on 2nd Attempt 02
   Other:_____ 03

2. Reason for Refusal to Participate:

   Illness 02
   Not interested 03
   No time available 04
   Opposed to study 05
   Impairment (specify)_____ 06
   Foreign language 07
   Other (specify)_____ 08

3. Strength of refusal:

   Mild, no hostility 01
   Firm but not hostile 02
   Hostile 03

4. Demographic/Refusal Questionnaire done:

   Yes 01
   No 02
   Refused 03

5. Is this person a candidate for a 2nd attempt for participation?

YES 01
NO 02
Reason:

Not Applicable 03

Comments:

6. When would be the best time to convert this refusal?
(MM/DD/YY and time of day; default = 3 months) ____ / ____ / ____

7. At which point did the refusal occur (following which statement, section of script, etc.)?

8. What methods did you use to persuade the subject to participate?

9. What kind of approach would be useful to convert this refusal?

10. Describe any other pertinent observations here.

PARTICIPANT WITHDRAWAL ASSESSMENT

(participant withdrew after initial agreement)

HANFORD THYROID DISEASE STUDY

March 3, 1995

	INITIALS	DATE	
			SUBJECT ID #: _____
CODED	_____	_____	
			COMPLETED BY: _____
KEYED	_____	_____	
			DATE OF
VERIFIED	_____	_____	WITHDRAWAL: __ __ / __ __ / __ __

1. Type of withdrawal:
   - Withdrawal on 1st Attempt 01
   - Withdrawal on 2nd Attempt 02
   - Other:_____ 03

2. Reason for withdrawal:
   - Illness 02
   - Not interested 03
   - No time available 04
   - Opposed to study 05
   - Impairment (specify)_____ 06
   - Foreign language 07
   - Other (specify)_____ 08

3. When did participant withdraw:
   - Before CATI 01
   - During CATI 02
   - When scheduling clinic appointment 03
   - During IP interview 04
   - During Blood draw 05
   - During thyroid US or exam 06
   - During FNA 07
   - After Clinic appointment 08
   - Other (specify _____) 09

4. Strength of withdrawal:
   - Mild, no hostility 01
   - Firm but not hostile 02
   - Hostile 03

5. Demographic/Refusal Questionnaire:
   - Yes 01
   - No 02
   - Refused 03

6. Is participant a candidate for a 2nd attempt for participation? (Only applicable if participant withdraws after 1st attempt)
   - YES 01
   - NO 02
     Reason:
   - Not Applicable 03

7. If answer to #5 is YES, when would be the best time to convert this refusal? (MM/DD/YY; Default = 3 months from first attempt)

   _____ / _____ / _____

8. What methods did you use to persuade this subject?

9. Describe any other pertinent observations or suggestions for converting this refusal.

CALENDAR OF EVENTS

May, 1995

Hanford Thyroid Disease Study
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-425
Seattle, Washington 98104

1-800-638-4837

INSTRUCTIONS

Because we are asking you to recall details about your family's life during 1939 through 1957, we have developed this **Calendar of Events** to help you remember some of the information we will want to know about your family during this time. The following two pages list some events that may have happened in your family in 1939, the 1940's and 50's. However, only you or your close friends or relatives will know the kinds of events and dates that will be most helpful in remembering the details of your lives.

As you read through this calendar, please take some time to think about events we have noted on the calendar year pages and write down the events important in your own family history during these years. There is room for your notes at the bottom of each calendar page. You may first want to write down the important events that you recall, and then go back and add the approximate dates when these events occurred. This may be a good time to bring out the family scrapbooks, photo albums, old letters or baby books, or to talk with friends and family about your lives in 1939, the 1940's and 50's. This **Calendar of Events** is for ***your*** use. We will not be asking you to return it to us.

This **Calendar of Events** may be helpful for you to review before filling out the enclosed **Residence History Questionnaire**. We will also ask that you have this **Calendar of Events** with you when we conduct your phone interview as it will be helpful for you to refer to it throughout the interview.

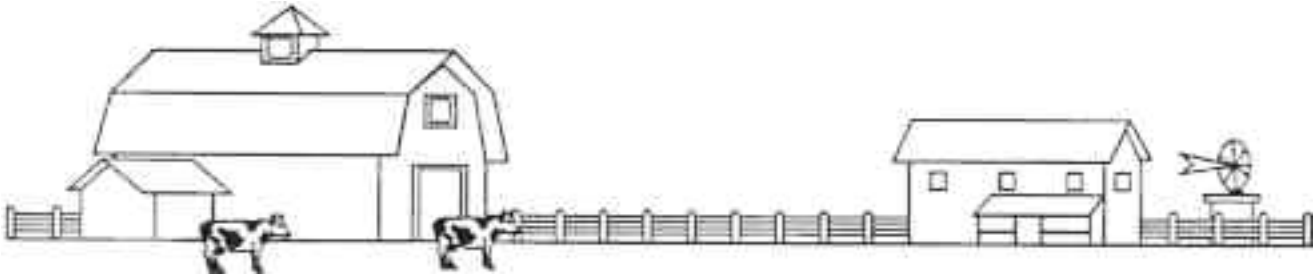
Please keep this calendar until you have completed the phone interview.

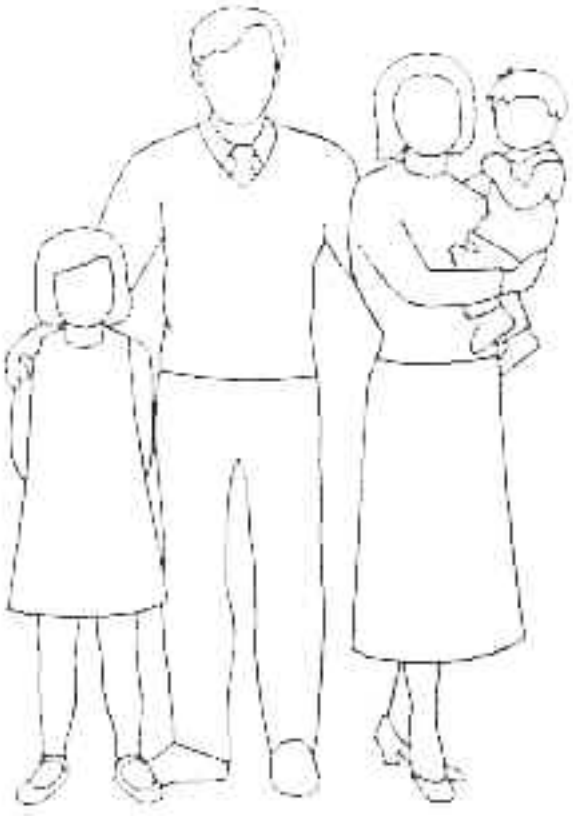
Thank you for taking the time to review this packet!

YOUR LIFE BETWEEN 1939 and 1957:

YOUR HOME

- Did your family move between 1939-1957? Where? When?
- What kind of house did you live in?
- Did you have farm animals or pets?
  What were their names?
  When did you have them?
- Did you build onto your home, like adding a garage or fence?





YOUR FAMILY and FRIENDS

- When were your children born?
  Where did you live then?
- Did someone start a new job?
  Or retire?
- When did your children start school?
  Where were you living then?
- Did family, friends, or neighbors move? When?
- Were children born to family or friends? When?
- Were family or friends wed? Divorced? When?
- Was there a death in the family or among friends?
  When?

YOUR LIFE BETWEEN 1939 and 1957:

THE WAR

- Did a friend or relative join the military? Who? When?
- Did family or friends return from military service? Who? When?
- Where were you when Pearl Harbor was bombed? (December, 1941)
  On V-E Day? (May, 1945) or V-J Day (August, 1945)

SPECIAL OCCASIONS

- Do you recall a special anniversary?
- Where did your family gather for holidays?
  Which holidays did you celebrate?
- Did you take vacations? Where? When?
- Did someone graduate from school? from college? Who?
  When?

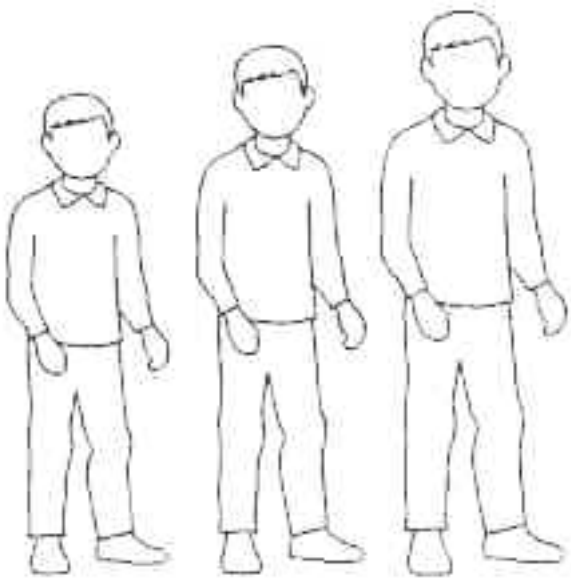
SOMETHING OLD, SOMETHING NEW

- Did your family purchase a new car or appliance? What kind? When?
- When did you first get indoor plumbing?
- Did your family get a new radio?
  or television?

LIFE THROUGH 1957:

HEALTH and GROWING UP

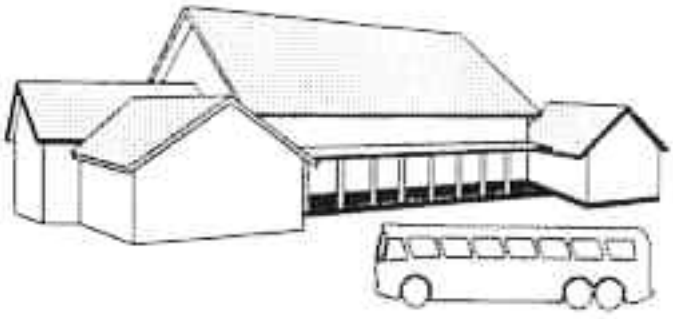
- When did he/she . . .
  start eating solid food?
  get first baby tooth?
  get first adult tooth?
  begin walking?
- What were his/her first words?
  When did he/she first talk?
- Which childhood illnesses did he/she have? Measles? Mumps? Chicken Pox? When?
- Did this child have other illnesses?
  What? When?



HOME LIFE

- Were there other children in the family? When were they born?
- When did this child move from a crib to a bed? Did he/she share a room?
- Did this child have a pet? When?
- When did he/she learn to ride a bicycle?

SCHOOL DAYS



- When did this child begin to read?
- What were this child's favorite after-school activities?
- Did this child join Scouts?
- When did this child change schools?

TOP STORIES OF 1939

* WORLD WAR II BEGINS IN EUROPE - GERMANY INVADES POLAND *
* NEW YORK WORLD'S FAIR *
* U.S. ECONOMY BOOMING FROM EUROPEAN ORDERS FOR ARMS AND WAR EQUIPMENT *

WASHINGTON STATE NEWS

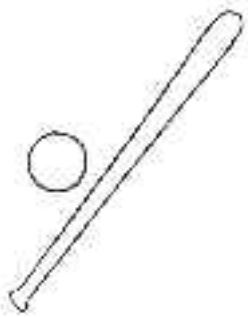
* Boeing in full war production *
* John Grant Kelly established continental canning company in Walla Walla, bringing many jobs to area *

TRENDS & PERSONALITIES

* Baseball game is first televised in U.S. *
* Nylon stockings first appear *
* John Steinbeck wins Pulitzer Prize for Grapes of Wrath *

POPULAR SONGS and MOVIES

* Roll out the Barrel *
* God Bless America *
* Over the Rainbow *
* Wizard of Oz *
* Gone with the Wind *
* Goodbye Mr. Chips *



Memorable Events of 1939

Write your memorable events here,
along with the dates

TOP STORIES OF 1940

* WW II: GERMANY INVADES DENMARK, NORWAY, LOW COUNTRIES, FRANCE and BRITAIN *
* TROTSKY ASSASSINATED IN MEXICO ON STALIN'S ORDERS *
* ROOSEVELT RE-ELECTED FOR 3rd TERM *
* VIGOROUS ISOLATIONISM SLOGAN: "THE PEOPLE SAY NO TO WAR" *

WASHINGTON STATE NEWS

* "Galloping Gertie" suspension bridge over Narrows of Puget Sound collapses in wind, dropping 200 feet *
* Mercer Island Floating Bridge Opens *

TRENDS & PERSONALITIES

* James Stewart wins Best Actor Oscar for Philadelphia Story *
* Ernest Hemingway's For Whom the Bell Tolls published *
* Jack Dempsey retires *
* Duke Ellington, popular composer and jazz pianist *

POPULAR SONGS and MOVIES

* You are My Sunshine *
* How High the Moon *
* When You Wish Upon a Star *
* Grapes of Wrath *
* Disney's Fantasia *
* Rebecca *

Memorable Events of 1940

Write your memorable events here,
along with the dates

TOP STORIES OF 1941

* Dec. 7: JAPANESE BOMB PEARL HARBOR *
* Dec. 8: U.S. DECLARES WAR ON JAPAN *
* Dec. 11: U.S. DECLARES WAR ON GERMANY and ITALY *
* U.S. SAVINGS BONDS AND STAMPS GO ON SALE *

WASHINGTON STATE NEWS

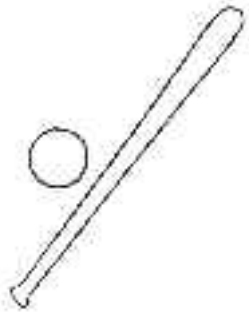
* Tri-Cities: July temp hits 115;
August and September rains destroy hay crop and damages grape crop *
* TriCities: Blackouts ordered in December *

TRENDS & PERSONALITIES

* F. Scott Fitzgerald's The Last Tycoon *
* Joe DiMaggio sets record hitting safely in 56 straight games *

POPULAR SONGS and MOVIES

* Deep in the Heart of Texas *
* Chattanooga Choo-Choo *
* Citizen Kane *
* How Green Was My Valley *
* Sergeant York *
* Suspicion *



Memorable Events of 1941

Write your memorable events here,
along with the dates

TOP STORIES OF 1942

* RATIONING BEGINS *
* WAGES ARE FROZEN *
* AMERICANS DEFEAT JAPANESE AT MIDWAY *
* Oct.: GUADALCANAL *

WASHINGTON STATE NEWS

* Army begins work on Walla Walla airport *
* Pacific War Time Implemented *
* White Bluffs High School burned; Students moved to Hanford High *

TRENDS & PERSONALITIES

* Joe Louis knocks out Buddy Baer to retain world heavyweight boxing crown *

POPULAR SONGS and MOVIES

* White Christmas *
* Holiday Inn *
* Bambi *
* That Old Black Magic *
* White Cliffs of Dover *

Memorable Events of 1942

Write your memorable events here,
along with the dates

TOP STORIES OF 1943

* July: MacARTHUR LAUNCHES ALLIED OFFENSE IN THE PACIFIC *
* RATIONING CONTINUES *
* BATTLE OF THE BISMARCK *

WASHINGTON STATE NEWS

* Building of Hanford Begins *
* McCaw General Hospital Opens *
* Town of White Bluffs Abandoned *

TRENDS & PERSONALITIES

* Jake La Motta beats Sugar Ray Robinson *
* Charlie Chaplin marries Oona O'Neill *
* Zoot Suit becomes popular *

POPULAR SONGS and MOVIES

* Casablanca *
* Jane Eyre *
* For Whom the Bell Tolls *
* I'll Be Seeing You *
* Mairzy Doats *
* Oh, What a Beautiful Mornin' *

Memorable Events of 1943

Write your memorable events here,
along with the dates

TOP STORIES OF 1944

* June: D-DAY/NORMANDY *
* PRESIDENTIAL ELECTIONS: FDR vs. DEWEY *
* BATTLE OF THE BULGE *
* COST OF LIVING IN U.S. RISES ALMOST 30% *

WASHINGTON STATE NEWS

* December: Hanford Starts Production *

POPULAR SONGS and MOVIES

* To Have and Have Not *
* Going My Way *
* Gaslight *
* Lifeboat *
* Don't Fence Me In *
* Rum and Coca-Cola *
* Accentuate the Positive *
* Sentimental Journey *

Memorable Events of 1944

Write your memorable events here,
along with the dates

TOP STORIES OF 1945

* February: IWO JIMA *
* April: FDR DIES *
* May: GERMANS SURRENDER - V-E DAY *
* August: BOMBING OF HIROSHIMA and NAGASAKI *
* August: JAPAN SURRENDERS - V-J DAY *

TRENDS & PERSONALITIES

* Bebop comes into fashion *
* Rocky Graziano, Boxer of the Year *
* Carousel hits Broadway *

POPULAR MOVIES

* Lost Weekend *
* Spellbound *
* Mildred Pierce *

Memorable Events of 1945

Write your memorable events here,
along with the dates

TOP STORIES OF 1946

* NUREMBURG TRIAL VERDICT REACHED *
* 9 NAZI WAR CRIMINALS HUNG *

WASHINGTON STATE NEWS

* McCaw Hospital Closed *

TRENDS & PERSONALITIES

* John D. Rockefeller, Jr. donates $8.5 million to U.N. *
* H.G. Wells dies *
* Benjamin Spock, M.D.'s Baby and Child Care published *

POPULAR SONGS and MOVIES

* Best Years of Our Lives *
* The Yearling *
* It's a Wonderful Life *
* Notorious *
* Ole Buttermilk Sky *
* Zip-a-dee-doo-dah *

Memorable Events of 1946

Write your memorable events here,
along with the dates

TOP STORIES OF 1947

* RELIEF DRIVE FOR EUROPEAN JEWS *
* OVER PRESIDENT TRUMAN'S VETO, U.S. CONGRESS PASSES TAFT-HARTLEY ACT, RESTRICTING RIGHTS OF LABOR UNIONS *

TRENDS & PERSONALITIES

* Al Capone dies *
* American, Jack Kramer, wins Wimbledon *
* Henry Ford dies *

POPULAR SONGS and MOVIES

* Gentleman's Agreement *
* Miracle on 34th Street *
* Almost Like Being in Love *

Memorable Events of 1947

Write your memorable events here,
along with the dates

TOP STORIES OF 1948

* BERLIN BLOCKADED; U.S. RESPONDS WITH AIRLIFT *
* TRUMAN ELECTED *
* April: FOREIGN ASSISTANCE ACT PASSED *
* INJUNCTION PREVENTS NATION-WIDE RAIL STRIKE *

WASHINGTON STATE NEWS

* Pasco Land Raffle *
* Freedom Train in Walla Walla *
* Tri-Cities Memorial Day Flood *

TRENDS & PERSONALITIES

* Babe Ruth dies *
* Joe Louis retires after fighting 25 title bouts *

POPULAR SONGS and MOVIES

* The Red Shoes *
* The Fallen Idol *
* Hamlet *
* All I Want for Christmas is My Two Front Teeth *
* Buttons and Bows *

Memorable Events of 1948

Write your memorable events here,
along with the dates

TOP STORIES OF 1949

* UNIV OF CALIFORNIA REQUIRES ALL FACULTY TO TAKE ANTI-COMMUNIST OATH *
* BERLIN BLOCKADE LIFTED *
* FIGHTER PLANE HITS AIRLINER -- 55 KILLED *

WASHINGTON STATE NEWS:

* FHA renegs on Veteran Farm Loans *

TRENDS & PERSONALITIES

* The McCarthy Years Begin *

POPULAR SONGS and MOVIES

* Twelve O'Clock High *
* Sands of Iwo Jima *
* The Third Man *
* Some Enchanted Evening *
* Diamonds are a Girl's Best Friend *
* Rudolph the Red Nosed Reindeer *

Memorable Events of 1949

Write your memorable events here,
along with the dates

TOP STORIES OF 1950

* KOREAN WAR BEGINS *
* JOE McCARTHY CHARGES THAT COMMUNISTS HAVE INFILTRATED STATE DEPARTMENT *
* BLIZZARD KILLS 250 NATIONWIDE *
* MacARTHUR NAMED HEAD OF FORCES IN KOREA *

WASHINGTON STATE NEWS

* Yakima River Frozen; Floods Follow *

TRENDS & PERSONALITIES

* McCarthyism Continues *
* Ray Bradbury's Martian Chronicles published *
* Al Jolson dies *

POPULAR SONGS and MOVIES

* Sunset Boulevard *
* All About Eve *
* If I Knew You Were Coming, I'd Have Baked a Cake *
* Mona Lisa *
* Ragg Mopp *

Memorable Events of 1950

Write your memorable events here,
along with the dates

TOP STORIES OF 1951

* PRICES AND WAGES ARE FROZEN TO CURB INFLATION *
* TRUMAN STRIPS MacARTHUR OF COMMAND IN FAR EAST *
* JULIUS AND ETHEL ROSENBERG SENTENCED TO DEATH FOR ESPIONAGE *

WASHINGTON STATE NEWS

* Chief Joseph Jr High School Opens *

TRENDS & PERSONALITIES

* William Randolph Hearst dies *
* JD Salinger's Catcher in the Rye published *
* Leadbelly dies *

POPULAR SONGS and MOVIES

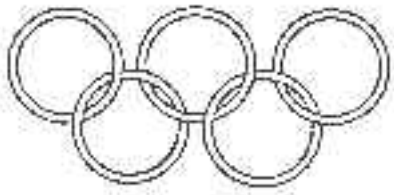
* African Queen *
* An American in Paris *
* A Streetcar Named Desire *
* Getting to Know You *
* Shrimpboats *
* In the Cool Cool Cool of the Evening *

Memorable Events of 1951

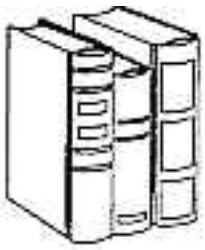
Write your memorable events here,
along with the dates

TOP STORIES OF 1952

* KOREAN WAR CONTINUES *
* EISENHOWER ELECTED *
* HELSINKI OLYMPICS *



TRENDS & PERSONALITIES



* Albert Schweitzer wins Nobel Peace Prize *
* Capote's The Grass Harp published *
* Hemmingway's Old Man and the Sea published *

POPULAR SONGS and MOVIES

* High Noon *
* The Greatest Show on Earth *
* Limelight *
* Your Cheatin' Heart *
* I Saw Mommy Kissing Santa Claus *

Memorable Events of 1952

Write your memorable events here,
along with the dates

TOP STORIES OF 1953

* QUEEN ELIZABETH II CROWNED *
* U.S. WITHDRAWS 2 DIVISIONS FROM KOREA *
* ROSENBERGS EXECUTED *
* KOREAN ARMISTICE SIGNED *

TRENDS & PERSONALITIES

* Ian Fleming's Casino Royale published *
* Stalin dies *
* Enforced desegregation begins *

POPULAR SONGS and MOVIES

* From Here to Eternity *
* Shane *
* Roman Holiday *
* Doggie in the Window *
* Stranger in Paradise *

Memorable Events of 1953

Write your memorable events here,
along with the dates

TOP STORIES OF 1954

* U.S. SIGNS PACT WITH NATIONALIST CHINA *
* JOE McCARTHY'S TELEVISED HEARINGS SEEK TO PROVE COMMUNIST INFILTRATION; HEARINGS LATER CONDEMNED BY SENATE *
* APRIL: 1ST H-BOMB TEST ON NATIONAL T.V. *

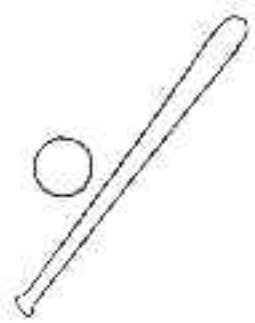
WASHINGTON STATE NEWS

* 4-Lane Highway Linking Pasco and Kennewick Opens *

TRENDS & PERSONALITIES

* Joe DiMaggio marries Marilyn Monroe *
* Willie Mays wins batting title *

POPULAR SONGS and MOVIES



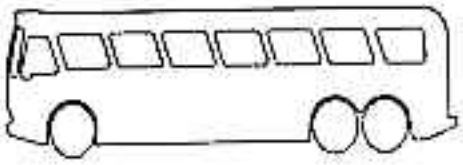
* On the Waterfront *
* Rear Window *
* Seven Brides for Seven Brothers *
* Mr. Sandman *
* Three Coins in the Fountain *

Memorable Events of 1954

Write your memorable events here, along with the dates

TOP STORIES OF 1955

* April: CHURCHILL RESIGNS *
* PANAMA AGREES TO COOPERATE OVER CANAL ISSUES *
* MONTGOMERY, ALABAMA BUS BOYCOTT *



WASHINGTON STATE NEWS

* Northern Pacific Railroad Yard Opens in Pasco *

TRENDS & PERSONALITIES

* April: Albert Einstein dies *
* September: James Dean dies *
* Sugar Ray Robinson wins boxing championship *

POPULAR SONGS and MOVIES

* Marty *
* Seven Year Itch *
* East of Eden *
* Rock Around the Clock *
* Yellow Rose of Texas *
* Love is a Many Splendored Thing *

Memorable Events of 1955

Write your memorable events here,
along with the dates

TOP STORIES OF 1956

* SALK POLIO VACCINE DEVELOPED *
* December: JAPAN ADMITTED TO U.N. *
* June: STEEL STRIKE *
* EISENHOWER RE-ELECTED *
* OLYMPIC GAMES HELD AT MELBOURNE *

TRENDS & PERSONALITIES

* Martin Luther King Jr. emerges as leader in fight for desegregation *
* Elvis Presley gains popularity *

POPULAR SONGS and MOVIES

* The Ten Commandments *
* The King and I *
* Giant *
* Blue Suede Shoes *
* Hound Dog *
* Que Sera Sera *

Memorable Events of 1956

Write your memorable events here,
along with the dates

TOP STORIES OF 1957

* June: SPUTNIK LAUNCHED *
* CUBAN SOLDIERS JOIN CASTRO REBELS *
* DESEGREGATION CRISIS IN LITTLE ROCK, ARKANSAS *

TRENDS & PERSONALITIES

* Joseph McCarthy Dies *
* Jimmy Hoffa charged, acquitted, & elected head of Teamsters *
* West Side Story hits Broadway *

POPULAR SONGS and MOVIES

* Bridge on the River Kwai *
* Peyton Place *
* Twelve Angry Men *
* 76 Trombones *
* Love Letters in the Sand *

Memorable Events of 1957

Write your memorable events here,
along with the dates

Thank You!

*Thank you for taking the time to review this **Calendar of Events**. We hope it was helpful and enjoyable.*

Please keep this calendar until you have completed the telephone interview, as it may help to make the interview go more quickly and easily.

RESIDENCE HISTORY QUESTIONNAIRE

Thank you again for agreeing to participate in this study. The first thing you can do is complete this questionnaire to provide information about places where the mother and child lived.

Please read the instructions below before starting. Remember, if you have any questions or need assistance do not hesitate to call our office at 1-800-638-4837. We will be happy to help.

INSTRUCTIONS:

1. This questionnaire has two sections:
   a. MOTHER'S SECTION - where the mother lived while pregnant with and breast-feeding the child
   b. CHILD'S SECTION - where this child lived from birth through 1957

   Start with the date already written on the top line for each section.
2. List residences over the entire time period from the starting date through 1957. If you do not recall addresses or dates, perhaps it is written somewhere: On old letters, old driver's licenses, or tax records. Other people may also be able to help you. It is all right to ask them. If you don't know an exact date, you may recall the month, season, or year. Try to be as exact as possible.
3. List the address and town for each residence. Also list the county, if known, for each residence. If there was no street address, write down the mailing address (for example, Route #1, Box 3) and the location (Lincoln Road between Oak and Alder Streets). If a residence was located in a rural area, please give the section, township, and range.
4. If there was a time when the family was between residences, indicate the dates and where the family stayed, just as with all the other residences.
5. If you need more space, please contact our office immediately at 1-800-638-4837. We will send you additional pages.
6. After you have completed the questionnaire, separate the sheets. Please return the white (top) copies of the questionnaire in the enclosed return envelope, to the HTDS office within one week. We will schedule your telephone interview after we have received your completed questionnaire.
7. The yellow (second) pages of the questionnaire are for you to keep. They will be used later during the telephone interview, so it will be important to have them available to use then.
8. Please use a ball-point pen when filling out the questionnaire.

HANFORD THYROID DISEASE STUDY

RESIDENCE HISTORY QUESTIONNAIRE - MOTHER'S SECTION

WHERE MOTHER LIVED WHILE PREGNANT/BREAST-FEEDING

DATE	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY

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HANFORD THYROID DISEASE STUDY

RESIDENCE HISTORY QUESTIONNAIRE - CHILD'S SECTION

WHERE CHILD LIVED THROUGH 1957

DATE OF BIRTH	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY
DATE MOVED TO	ADDRESS/LOCATION	TOWN/STATE	COUNTY

INTERVIEW BOOKLET

May, 1995

Hanford Thyroid Disease Study
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-425
Seattle, Washington 98104

1-800-638-4837

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page 2

FORM APPROVED:

OMB NUMBER: 0920-0296

EXP. DATE: May 31, 1998

Public reporting burden of this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to PHS Reports Clearance Officer; ATTN: PRA (0920-0296); Hubert H. Humphrey Bldg., Room 737-F; 200 Independence Avenue S.W., Washington, D.C. 20201

page 3

This interview will be about

_____

from birth through 1957.

We really appreciate your help with this important study. As we discussed over the telephone, the purpose of this interview will be to find out about events and food consumption in 1939, the 1940s and 1950s, during this child's youth.

We know that these events may be difficult to recall, and that is why we have sent you this booklet. It is important that the information you give us about this child's youth be as accurate as possible. Each section in this booklet asks you to remember some important details about your life in 1939, the 1940s and 1950s that will help you to recall some of the information we will be asking about over the phone. We have found that if people go through these materials before the interview, jotting down some notes, the interview goes more easily and quickly for them. This may be a good time to bring out the family album, old letters, scrapbooks or baby books. Please feel free to discuss any or all of the questions in this booklet with family or friends, or anyone who might help you to remember 1939, the 1940s and 1950s.

It will be helpful to refer to your copy of the **Residence History Questionnaire** and **Calendar of Events** you have already completed while reviewing this booklet.

This booklet was designed to help you remember things about you and this child through 1957. It is for your use. We will not be asking you to return this booklet.

Keep in mind that there is no right or wrong answer.

page 4

About the Raw Milk Your Family Drank

Did Your Family Drink Raw Milk?
Where Did Your Family Get Milk?

Include any raw (unprocessed) milk which your family may have drunk. Unlike the processed milk which may have been available from dairies or grocery stores, 'raw' or 'unprocessed' milk is milk which has not been treated in any way; not pasteurized, not homogenized.

Many families had a few cows or goats, sometimes to help reduce food costs. In some cases it may have been necessary to keep animals in order to receive a home or farm loan. Perhaps neighbors or relatives with cows or goats provided milk to your family.

For unprocessed or raw milk, we would like to learn about what the animal ate and drank, and where the animal lived. You may know, or there may be someone you can ask, like a family member or neighbor.

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page 5

THESE QUESTIONS MAY HELP YOU TO RECALL WHERE YOUR FAMILY GOT RAW MILK	WHERE YOUR FAMILY GOT RAW MILK: 1939 through 1957
• Did your family have a cow or goat? • Did your neighbors or relatives have a cow or goat that provided milk to your family? • Did the milking animal live on your property? On a neighbor's property? • Did it have room to graze? • Was the weather too harsh for the animal to graze year round? • What else did the animal eat? • Where did the animal's drinking water come from? A well? Pond? Stream or Creek? Rainwater cistern? • Did the animal's water come from the same place as your	

family's
drinking water?

- Did anything about the animals
your family got raw milk from ever
change, like where they grazed?

- Did you get milk from a different farm?

page 6

About the Processed Milk Your Family Drank

Did Your Family Drink Processed Milk?
Where Did Your Family Get Milk?

By processed milk, we mean any milk that has been homogenized and/or pasteurized. ***When we refer to "fresh" milk, do not include milk that was canned or powdered***. This would have been milk that you may have purchased from a grocery store or a local dairy. Even families that had their own milk cows or goats sometimes supplemented their supply with milk they purchased.

To the right is a listing of dairies which may have provided milk in the area you lived during these years. It may be helpful to first circle the brand names which you recall having purchased, and then note the dates you used these brands, or the places you lived when you bought these brands.

If you can't remember the brand name, can you recall something else about the brand; their trademark or the colors they used on the package, for example?

Brands of Milk

Calhoun's Dairy	Scudder Ranch Dairy
Carnation	Selah Home Dairy
Cascade Golden Star	Shady Lawn Creamery
Connel Dairy	Spreen's
Darigold	Spring Brook Dairy
DeBoer Farm Dairy	Swanson's Dairy
Depping's Dairy	Sweet Clover
Detloff	Thorp's Creamery
Diversity Farm	Tomlinson's
Duff's Creamery	Twin City Creamery
Fairview Guernsey Dairy	Union Gap Dairy
Golden Guernsey Dairy	Walla Walla College Dairy
Hulburt Dairy	Walla Walla Dairymen's Association
Ingram's Dairy	Washington State Penitentiary
Lloyd Meyer	Westlawn Dairy
Lower Naches	Wiley City Dairy
Lucerne	Willow Point
Mack's Creamery	Wilmont's Morning Sun
Maid-O-Clover	Yakima City Creamery
Maple Leaf	Yakima City Dairy
Mary-O Dairy	Yakima Dairymen's Association
May's Dairy	Yakima Poultry and Egg Co.
Mayflower	Young's

McColum's/Reeseman's Milk Products Company Morning Milk Mountain View Dairy Naches Dairy Percy Clark's Dairy Puritan Reeseman'sRitzville Dairy	LIST ANY OTHER BRAND HERE (DESCRIBE LABEL OR SLOGAN):

page 8

About when this Child was an Infant

One of the first questions we will be asking is when this child was born. When we refer to "this child", we mean the subject, who was born between 1940 and 1946. We have written his/her name on the first page of this booklet.

In the first part of the telephone interview, we will be trying to establish dates that will be used throughout the interview. This is where it may be especially helpful if you take the opportunity to note important dates on the Calendar of Events.

In addition to your child's date of birth, we are interested in whether this child was breast-fed (nursed), how old this child was when he/she first began drinking milk (other than breast milk), and first began eating foods other than milk.

Feelings about the age at which a child should begin eating solid food, or even whether a child should be breast-fed, have changed over the years. As with all questions we ask, remember that ***there is no right or wrong answer.***

page 9

THESE QUESTIONS MAY HELP YOU REMEMBER SOME SPECIFIC DATES FROM WHEN THIS CHILD WAS AN INFANT:	ABOUT WHEN THIS CHILD WAS AN INFANT:
• When was this child born? • Was this child born in the Spring, Summer, Autumn, or Winter? • Was he/she breast-fed (nursed)? Until what age? • Did this child need night feedings to help him/her sleep? • When this child first began drinking milk other than breast milk, how much of his/her diet was:	

Breast milk?
Canned or powdered milk?
Fresh processed milk?
Fresh raw milk?

- Did this child have an allergy or
intolerance to any type of milk?

- When this child first began eating foods other than milk, how
much of his/her diet was:
Solid food, such as cereal?
Breast milk?
Canned or powdered milk?
Fresh processed milk?
Raw milk?

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page 10

About the Milk Your Family Drank

This includes raw and processed milk, chocolate milk or cocoa, and buttermilk, but does not include canned or powdered milk. Cream, butter, and cottage cheese are some examples of the dairy products we will ask about later. If you are not sure whether something is considered 'milk' or a 'dairy product', remember that the interviewer will be glad to answer any questions for you.

Did you drink milk while you were pregnant with this child?

In talking with people, we have found that some people have special memories of the milk they drank while they were pregnant and breast-feeding. During the telephone interview, we will be asking about how much and which types of milk you drank. It may be helpful to you if you think about how much milk you drank before you were pregnant, to help recall if you drank more or less milk while you were pregnant and breast-feeding. Later, we will ask about dairy products you may have eaten. But for now, we are interested only in the milk you drank.

What kind of milk did this child drink?
How much milk did this child drink?

We are interested in finding out how much and which kinds of milk this child drank. We will also be asking you about significant changes in this child's diet, beginning with the milk he/she drank.

It may be helpful to you to remember back to when this child was an infant, then through 1957.

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THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT THE MILK YOUR FAMILY DRANK	ABOUT THE MILK YOUR FAMILY DRANK: 1939 through 1957
• What types of milk did your family drink? - Powdered? Canned? - Fresh, processed milk? - Raw milk? - Cow or goat milk? • Did anyone in your family have an allergy to any type of milk? Who? • What was your family's favorite kind of milk?	

- Was this kind of milk always available?
- Did rationing during the war affect what types of milk were available?
- Do you recall how often milk came into the house? Daily? Weekly? How big were the containers? Gallon jugs? Quart bottles?
- Did you use a different kind of milk for cooking than for drinking? What kind of milk did you use?
- Were foods that were prepared with milk a regular part of meals? Such as
  - Pancakes at breakfast?
  - Cream soups at lunch?
  - Gravy or casserole at dinner?

HERE ARE SOME QUESTIONS WHICH MAY HELP YOU RECALL HOW MUCH MILK YOU DRANK WHILE YOU WERE PREGNANT AND BREAST-FEEDING:	ABOUT THE MILK YOU DRANK WHILE YOU WERE PREGNANT AND BREAST-FEEDING
• Did you drink more milk than usual while you were pregnant, perhaps on the recommendation of a doctor or family member? • Were you likely to drink milk at every meal or just one or two meals a day? • Did you use milk over hot cereal? Cold cereal? • Was milk poured over fruit, such as strawberries or peaches? • Did you have milk for snacks? • Did you drink fresh raw milk? Fresh processed milk? Canned milk? Powdered milk? • Did you drink cow's milk? Goat's milk? Both?	

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THESE QUESTIONS MAY HELP YOU TO REMEMBER ABOUT THE MILK THIS CHILD DRANK:	ABOUT THE MILK THIS CHILD DRANK THROUGH 1957
• What different kinds of milk did this child drink? Fresh raw milk? Fresh processed milk? Powdered milk? Canned milk? Cow or goat milk? • Did he/she drink the same kind of milk all of the time? • Which was his/her favorite kind of milk? Was there always enough? • Did he/she drink a different type of milk away from home? • Did this child drink milk at every meal? Snacks? • Did he/she drink milk one glass at a time? Several glasses? • Did this child drink cocoa or	

chocolate milk? Warm milk?

- Was milk used on cold cereal? Hot cereal? Over fruit?
- Did this child's appetite for milk change gradually or dramatically?
  When?

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About the Dairy Products Your Family Ate

It may be helpful to you if you remember which foods were available to you. For example, if your family had a cow or a goat, perhaps fresh butter or ice cream was made from the raw milk.

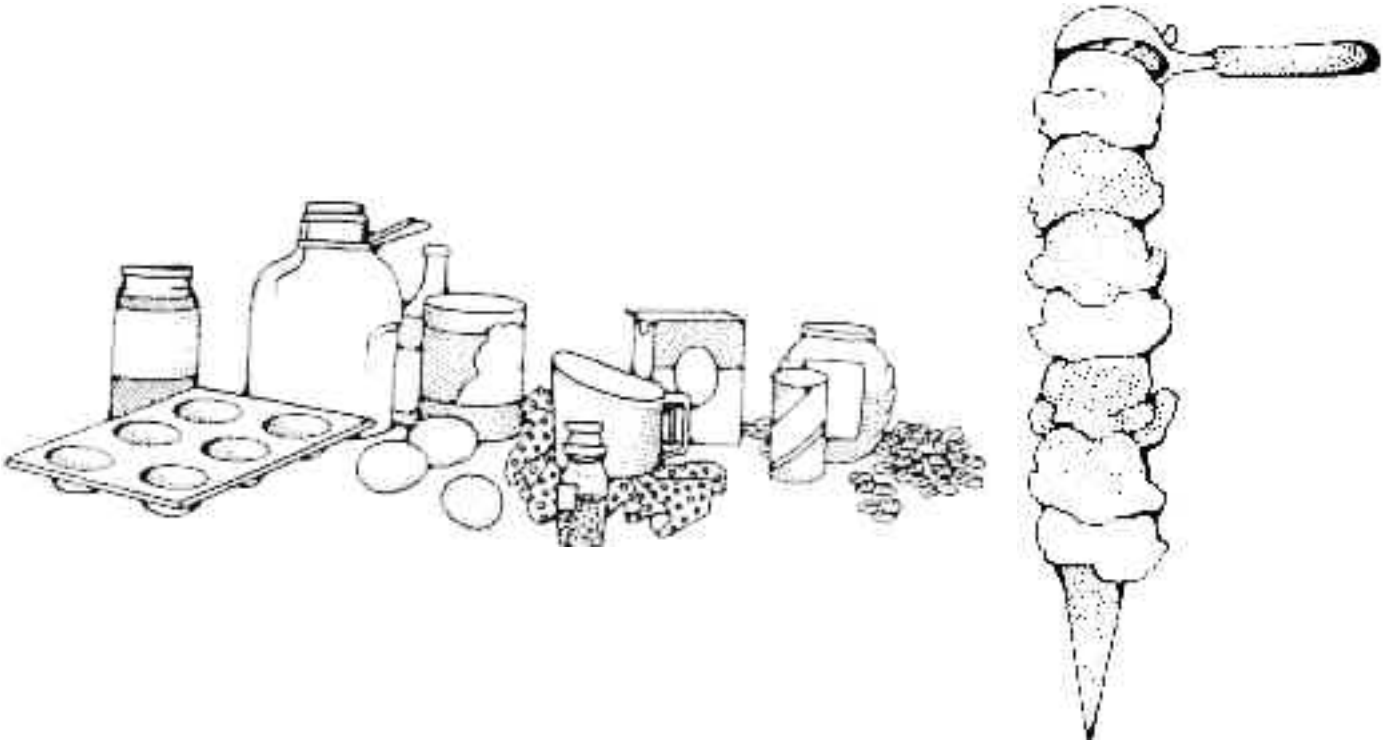
Fresh Dairy Products are those which had not been aged and have a shorter shelf life. *Fresh Dairy Products* include:

Cream, Butter, Buttermilk, Ricotta Cheese, Cottage Cheese,

Ice Cream, Yogurt, and Sour Cream

but would **not** include hard cheese, like cheddar cheese, which is aged longer. If you are not sure if a certain type of dairy product is to be included, the interviewer will be glad to answer any questions during the phone interview.

In addition to the milk you and this child drank, we are interested in the dairy products you ate when you were pregnant with and breast-feeding this child; and those the child ate through 1957. As with milk, we will be asking how much was eaten and how it changed.



THESE QUESTIONS MAY HELP YOU TO REMEMBER ABOUT THE DAIRY PRODUCTS YOUR FAMILY ATE	ABOUT THE DAIRY PRODUCTS YOUR FAMILY ATE: 1939 through 1957

- Did your family or friends make:
  - Homemade ice-cream?
  - Butter?
  - Cottage Cheese?
  - Yogurt?

- Did you use dairy products, such as cream, in cooking:
  - Cream soups?
  - Casseroles?
  - Sauces or Gravy?

- Which dairy products were made from raw milk?

- Which were purchased at a store? (made from processed milk)?

- Did your family use butter, cream, or other fresh dairy products in making:
  - Biscuits?
  - Cakes, cookies or pies?
  - Waffles or pancakes?
  - Pudding or cream pies?

- Did you use butter for frying? For baking?

- Which other ways did you use dairy products in cooking?

THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT THE DAIRY PRODUCTS YOU & THIS CHILD ATE:	ABOUT THE DAIRY PRODUCTS YOU ATE WHILE YOU WERE PREGNANT AND BREAST-FEEDING	ABOUT THE DAIRY PRODUCTS THIS CHILD ATE THROUGH 1957
• Was butter used on: - Toast? - Sandwiches? - Waffles? - Pancakes? - Biscuits? - Cooked vegetables? • Was ice cream a regular part of dessert? • Was whipped cream a regular part of dessert? • Was cottage cheese or yogurt eaten? • Did you eat more dairy products while you were pregnant and breast-feeding? • Did this child's taste		

for dairy products change?
- How?
- When?

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VEGETABLES

Asparagus
Beet Greens
Broccoli
Brussels Sprouts
Cabbage
Cauliflower
Celery
Chard
Chicory
Chives
Collards
Dandelion Greens

Endive
Escarole
Kale
Lettuce
Mustard Greens
Parsley
Poke Greens
Romaine
Spinach
Turnip Greens
Watercress

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About the Vegetables Your Family Ate

In addition to dairy products, we are interested in a few other types of foods you and this child may have eaten. This first group we refer to as *Fresh Green and Leafy Vegetables*. The specific vegetables we are interested in are listed to the left. As you look at the list, it **may be helpful to cross-out those vegetables that your family never ate**. There are many vegetables which your family may have eaten which are not included on this list, tomatoes and corn, for example. **We are only interested in the vegetables specifically listed on the page to the left**. If you are not sure whether a vegetable is to be included, the interviewer will be glad to answer any questions during the phone interview.

We realize your family may not have eaten some of these vegetables, but as you look at the list, you may recall which vegetables were favorites that you or this child ate regularly. It may be helpful to you to remember which vegetables were available at the time. Perhaps you grew some in a 'Victory Garden' or purchased others at a grocery store. While your family may have eaten vegetables more at harvest time, they may have eaten canned or frozen vegetables year round. **When thinking about how much of these vegetables you and this child ate, consider just the time of year when each of those vegetables was fresh and in-season locally.**

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THESE QUESTIONS MIGHT HELP YOU TO RECALL WHERE YOUR FAMILY GOT THESE VEGETABLES:	**ABOUT THE VEGETABLES YOUR FAMILY ATE: 1939 through 1957**
• Were vegetables a regular part of your family's diet? Which ones? • Which of these vegetables were available to you? • Did your family have a vegetable or 'Victory' garden? Which of these vegetables did	

you grow? • Which years did you have a vegetable garden? • Were there some vegetables that grew well in your garden? Others that did not? • Did friends, relatives, or neighbors share produce from their gardens with your family? Which of these vegetables? • Which of these vegetables did you get from: - a local farm or roadside stand? - the grocery store? • Were there vegetables that you regularly had on hand? Which ones?	

THESE QUESTIONS MAY HELP YOU TO RECALL THE VEGETABLES YOU & THIS CHILD ATE:	ABOUT THE VEGETABLES YOU ATE WHILE PREGNANT AND BREAST-FEEDING	ABOUT THE VEGETABLES THIS CHILD ATE: Through 1957

• Which of these vegetables were favorites? • Were salads or coleslaw eaten with meals? • Did your family have a fresh vegetable plate at dinner? Lunch? Snacks? • Which of these vegetables were eaten raw? Which ones were eaten cooked? • Did you eat different vegetables while you were pregnant and breast-feeding? • Which vegetables were used for baby food? • Did this child's taste for vegetables change? In what way? When?		

FRUIT

TREE FRUITS:	BUSH and VINE FRUITS:
Apples Pears Apricots Peaches Fresh Prunes and Plums Cherries (do NOT include citrus fruits or bananas) 	Berries Grapes (do NOT include melons) 

About the Fruits Your Family Ate

In addition to the vegetables you and this child ate, we are interested in certain fruits you may have eaten during the time you were pregnant and breast-feeding, and those this child may have eaten through 1957.

The fruits we are interested in are listed to the left. ***As with the vegetables, you might want to cross-out those fruits which your family never ate***. We realize there are many fruits which your family may have eaten which are not included on this list, oranges or bananas, for example. ***We are only interested in the fruits specifically listed on the page to the left***. If you are not sure whether a fruit is to be included, the interviewer will be glad to answer any questions during the phone interview.

During the interview, questions will be asked separately about 'tree fruits' and 'bush or vine fruits'. On the following pages are questions which may help you to remember which, if any, of these fruits you and this child ate. Your family may have eaten these fruits at harvest time, or may have eaten canned fruit or preserves which would have been available year round. ***When thinking about how much of these fruits you and this child ate, consider just the time of year when each of those fruits was fresh and in-season locally.***

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THESE QUESTIONS MAY HELP YOU TO REMEMBER ABOUT THE FRESH FRUIT YOUR FAMILY ATE:	**ABOUT THE FRUIT YOUR FAMILY ATE: 1939 through 1957:**

- Which of these fruits were available?
- Which were grown in the area at that time?
- Did family or friends have an orchard? Which fruits were grown?
- Were there wild berries near your home?
- Did you grow fruit in your garden? Tree fruits? Berries or Grapes?
- Which of these fruits did you get from:
  - A local farmer?
  - Friends or neighbors?
  - Out of town relatives?
  - Grocery store?
- Did you make fresh fruit juice, or get fresh fruit juice from:
  - Friends or neighbors?
  - Grocery store?
  - Local farmer?
- Did you cook with fresh fruit, such as making applesauce or pies?

THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT THE FRUIT YOU & THIS CHILD ATE:	ABOUT THE FRUIT YOU ATE WHILE PREGNANT AND BREAST-FEEDING THIS CHILD:	ABOUT THE FRUIT THIS CHILD ATE: Through 1957
• Which of these fruits were eaten raw? Cooked? Canned? Dried? As preserves? • Which of these fruits were favorites? • Did either of you drink fresh fruit juice? • Was fruit a regular part of your diet? Of this child's diet? • Was fruit eaten for snacks or with meals? As dessert?		

• Did you make fresh baby-food, such as applesauce, when this child was an infant? • Did this child's taste or appetite for these fruits change? How? When?		

About the Free-Range Chicken Eggs Your Family Ate

"Free-Range" chickens are chickens that are not cooped-up all the time, but are allowed to roam and feed on whatever is on the ground.

This is the last section about your family's diet that we will be asking about.

THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT ANY FREE-RANGE CHICKEN EGGS YOUR FAMILY ATE	ABOUT THE FREE-RANGE CHICKEN EGGS YOUR FAMILY ATE:
• Did your family raise chickens? Did your friends, neighbors, or relatives raise chickens? • Were these chickens raised for their eggs? • Were these chickens allowed to roam free, feeding on what was on the ground? Or were they in a coop all the time? • Did you use these eggs in baked goods? Cakes or Cookies? Pies or Puddings? Biscuits, Pancakes, or Waffles? • Did you use these eggs in: Egg-salad? Deviled eggs? Potato or Macaroni Salad? Home-made mayonnaise?	

THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT ANY FREE-RANGE CHICKEN EGGS YOU AND THIS CHILD ATE	ABOUT THE FREE-RANGE CHICKEN EGGS YOU ATE WHILE PREGNANT AND BREAST-FEEDING	ABOUT THE FREE-RANGE CHICKEN EGGS THIS CHILD ATE: Through 1957
• Were these eggs a regular part of breakfast? For you? For this child? • Which foods made with these eggs did either of you eat? Egg salad? Deviled eggs? Potato Salad? Macaroni Salad? • When did this child first begin eating free-range chicken eggs? • Did this child's appetite for eggs change? In what way? When?		

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Your Medical History:

Various Tests and Procedures While You Were Pregnant With This Child

There are certain types of medical procedures that we are interested in which you may have had while you were pregnant. For example, you may have had an x-ray after an accident, a fluoroscopy, or an upper G.I. series to diagnose stomach problems. A fluoroscopy is a type of x-ray in which the doctor may stand next to the patient and observe parts of the body on a fluorescent screen like a TV set.

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THESE QUESTIONS MAY HELP YOU RECALL MEDICAL TREATMENTS OR PROCEDURES YOU MAY HAVE HAD WHILE PREGNANT:	ABOUT WHILE YOU WERE PREGNANT
• While you were pregnant did you see a physician for any reason not related to your pregnancy? What was the diagnosis? • While pregnant, did you suffer any injury or accident which may have required x-rays? • While pregnant, did you have any illnesses or conditions which may have required having a: - Barium Enema of the large intestine? - Upper GI series? - IVP of the kidneys? - X-ray of Pelvis, Chest, Back or Stomach? - Fluoroscopy of a part of the upper body? • Did you have a thyroid scan while you were pregnant?	

- While pregnant, were you given a radioactive substance, either orally or intravenously, in order to diagnose a medical problem?

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Your Medical History:

Thyroid Problems

It is important for us to know if you were diagnosed with thyroid disease at any time during your life prior to or during this pregnancy. For example, you may have at some time *before or during* this pregnancy been diagnosed with:

- Graves' Disease or Hyperthyroidism, which is an overactive thyroid
- Hypothyroidism, which is an underactive thyroid
- Thyroid tumor or lump, whether it was benign or malignant
- Goiter

There are a lot of different treatments for thyroid problems. ***Although we want to know if you were diagnosed with a thyroid problem before or during this pregnancy, it is only the treatments you received while pregnant with this child that are of interest here***. If you had a thyroid problem, perhaps you were on medication or received radiation treatment while pregnant.

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THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT ANY THYROID PROBLEMS:	ABOUT BEFORE OR DURING THIS PREGNANCY
• Did you take any thyroid medication while you were pregnant? For what condition? • Did you have radiation treatment to your thyroid while pregnant? What type? For what condition? • Did a physician tell you that you had Graves' Disease, an over-active thyroid, or hyperthyroidism? • Did a physician tell you that you had an under-active thyroid, or hypothyroidism? • Did a physician tell you that you had a lump or tumor on your thyroid? • Was this tumor or lump benign? Malignant? • Did you ever have goiter? • Which types of treatments were given for this thyroid problem? - Medication? - Radiation Treatment?	

This Child's Medical History to Age 15:

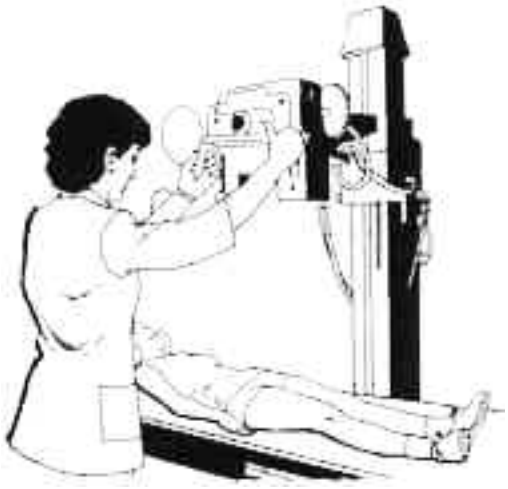
Diagnostic X-rays

There are several types of medical procedures this child may have had which we are interested in knowing about. For these procedures it will be helpful to know his/her age at the time, and how many times each procedure was repeated. ***Remember, we are only interested in his/her medical history up to age 15.***

First, we will be asking about any *diagnostic x-rays and x-ray treatments* he/she may have had. We are interested in x-rays of the upper body only. At the end of this booklet you will find a diagram of the human body; the shaded portion shows the areas of interest.

Diagnostic x-rays may have been taken for a number of reasons. Perhaps this child was being checked for broken bones, or the x-ray was used for screening purposes, such as a chest x-ray to detect tuberculosis. Whatever the reason, we would like to know if he/she ever had x-rays or fluoroscopies of the upper body, including the head (excluding dental x-rays), neck, and chest.

In trying to diagnose, for example a stomach problem, this child's doctor may have requested that the child have an upper G.I. series or IVP (intravenous pyelogram of the kidneys). These are also considered diagnostic x-rays.



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THESE QUESTIONS MAY HELP YOU REMEMBER ABOUT ANY DIAGNOSTIC X-RAYS THIS CHILD MAY HAVE HAD:	ABOUT THIS CHILD TO AGE 15
• Did he/she have any injuries or accidents which may have required x-rays? • Which part of the body was x-rayed? When? • Did this child ever have chest x-rays for pneumonia, tuberculosis, or another condition? When? • Did he/she have any digestive, stomach, bowel, or kidney problems? Did this problem require an IVP, Upper GI series, or a Barium	

Enema to diagnose it?

- How old was he/she when the diagnostic procedure was done?
- How many different times was the diagnostic procedure done?
- Were fluoroscopies of the upper body ever performed? If so, how many times?

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This Child's Medical History to Age 15:

X-ray Treatments

Like diagnostic x-rays, x-ray treatments may have been given for a number of reasons. Some conditions that children may have received x-ray treatments to the upper body included:

- Acne, ringworm, or scalp infection
- Enlarged tonsils or enlarged thymus
- Tuberculosis

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THESE QUESTIONS MAY HELP YOU REMEMBER IF THIS CHILD HAD X-RAY TREATMENTS TO THE HEAD OR UPPER BODY:	ABOUT THIS CHILD TO AGE 15
• Did he/she ever have a skin condition, such as ringworm or acne, which required x-ray treatments? • Did he/she receive x-ray treatments for - Enlarged Tonsils? - Enlarged Thymus? - Tuberculosis? • Who was your family doctor during the 1940's and 1950's? • Did this child have a pediatrician or different doctor than the rest of the family? • Did his/her physician have x-ray equipment at the office, or was it located at the hospital or another clinic? • How old was he/she at the time of the radiation treatments? • How often were these treatments repeated?	

This Child's Medical History to Age 15:

Other Diagnostic Procedures

In addition to x-rays used for diagnosing a problem, there is another area of diagnostic medicine which we are interested in. These include thyroid scans and what is referred to as diagnostic nuclear medicine (also called nuclear scans).

Diagnostic nuclear medicine is where a person takes a radioactive substance, either by mouth or by injection. The organ or area of interest is then scanned to evaluate its function.

THESE QUESTIONS MAY HELP YOU RECALL WHICH OTHER TYPES OF DIAGNOSTIC PROCEDURES THIS CHILD HAD	ABOUT THIS CHILD TO AGE 15

- Before the age of 15, did this child have a thyroid scan?
- Before the age of 15, did this child have a medical condition which required extensive diagnostic tests?
- Did this child have any other scans done, that is, taking a radioactive substance by mouth or by injection?
- How old was the child when the procedure was done?
- What was the reason for the procedure?
- Was the procedure done more than once?
  On how many different occasions?
- Under the direction of which physician?

This Child's Medical History to Age 15:

Thyroid Problems

It is important that we know whether this child was diagnosed with thyroid disease. These include:

- Graves' Disease or Hyperthyroidism, which is an overactive thyroid

- Hypothyroidism, which is an underactive thyroid
- Thyroid tumor or lump, whether it was benign or malignant
- Goiter

There are a number of treatments for thyroid problems. Some of these treatments are:

- Surgery
- Medication
- Radiation Treatment

If this child received a thyroid scan or was diagnosed or treated for thyroid disease before age 15, we will ask you to provide the name and address of this child's physicians.

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THESE QUESTIONS MAY HELP YOU TO REMEMBER ABOUT ANY THYROID PROBLEMS THIS CHILD MAY HAVE HAD:	**ABOUT THIS CHILD TO AGE 15**
• Did a physician ever say this child had Graves' Disease, an over-active thyroid, or hyperthyroidism? • Did a physician ever say this child had an under-active thyroid, or hypothyroidism? • Has a physician ever said this child had a lump or tumor on his/her thyroid?	

- Was this tumor or lump benign? Malignant?
- Was this child diagnosed with goiter?
- Which physician diagnosed the condition?
- Which types of treatments were given for this thyroid problem?
  - Medication?
  - Radiation Treatment?
  - Surgery?
- Was this child ever on thyroid medication?
- At what age was treatment given?
- Under the direction of which physician?

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This Child's Medical History to Age 15:

Dental X-rays

Unlike other diagnostic x-rays, dental x-rays are often taken as a matter of course, regardless of whether there is a particular problem.

As with the other sections, we are interested in this child's general dental history only to age 15.

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THESE QUESTIONS MAY HELP YOU TO RECALL THIS CHILD'S EARLY VISITS TO THE DENTIST:	ABOUT THIS CHILD TO AGE 15
• When did this child first see a dentist? • What prompted this child's first trip to the dentist? • How often did this child go to the dentist? - Annually? - As needed? How often was that? • Did this child have a lot of dental work done? - Fillings? - Braces?	

- Tooth extractions?
- Bridges?

- Were dental x-rays taken at every visit?
  Annually?
  Never?

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THANK YOU

Thank you for taking the time to review this booklet and to write down your notes.

The notes you have made should help to make the interview go more quickly and easily.

It is important that you have this **Interview Booklet** and the **Calendar of Events** on hand for your phone interview. Please also have a pen or pencil and paper within reach.

At the beginning of the interview the interviewer will ask you to take out an 8 ounce measuring cup to help determine amounts during the interview. (You may want to have one ready before the interview begins.)

There is still a great deal to be learned about the releases from Hanford, and the possible health effects to surrounding communities. It is important for you to remember that you could not have known about these releases or of any health risk at the time.

Thank you, again, for taking the time to review these materials.

IRB approved May 28, 1996

Meet the Johnsons

We have created this family, the Johnsons, to give you an idea of the types of questions which will be asked in the telephone interview. Below is a description of this family with information that would apply to this study. On the reverse side of this page are sample questions that the Johnsons would be asked in the telephone interview, along with the answers. The actual telephone interview contains many questions. This sample is designed to give you some idea of the types of questions which will be asked.

Fred and Ethel Johnson have three children:

Joey born in July of 1948
Susie born in May of 1946
Johnny born in August of 1943

Susie was randomly selected as a subject in this study.

The Johnsons lived in a small house in the city of Richland from 1940 to 1948. The water for their house in Richland was from a public water supply. They bought their produce at a grocery store, and had milk delivered to their house from a local dairy.

In the summer of 1948, the Johnsons moved to a larger home on a few acres in rural Walla Walla, where they had a large vegetable garden, and a few fruit trees. The family's drinking water came from one well, as did the water for their garden. The Johnsons new neighbors had a small farm and provided the Johnsons with raw cow's milk.

SAMPLE QUESTIONS

When living in Richland, did your family ever eat or drink:
Raw Cow's Milk? Raw Goat's Milk?
Processed Cow's Milk? Processed Goat's Milk?

All the milk we drank then was processed cow's milk.

When living in Walla Walla, did your family ever eat or drink:
Raw Cow's Milk? Raw Goat's Milk?
Processed Cow's Milk? Processed Goat's Milk?

When we moved to Walla Walla, we started drinking raw cow's milk. From then on, that's the only kind we drank.

When you moved to Walla Walla when Susie was 2 years old, how many 8 ounce glasses of raw cow's milk did she drink per day?

She drank small amounts, about 4 ounces at a time, and she had it at every meal and for snacks. That would be 5 times a day.

In December of 1957, how many 8 ounce glasses of raw cow's milk did Susie drink per day?

She was 11 years old then, and liked milk a lot. Probably about 5 glasses a day.

Between the time Susie was 2 and 11, were there significant changes in the amount of raw cow's milk she drank that you can recall?

Yes, about the time she started school. That was in the autumn of 1951. Then she drank at least 4 of those 8 ounce glasses each day

HANFORD THYROID DISEASE STUDY

DOSIMETRY QUESTIONNAIRE

April 11, 1995

INTRODUCTION

ESTABLISHING CONTACT WITH RESPONDENT:

Hello, may I speak to (RESPONDENT'S NAME)?

WHEN YOU CONFIRM THAT YOU HAVE THE RESPONDENT ON THE LINE, PROCEED TO PREPARE FOR THE INTERVIEW. IF THE RESPONDENT IS UNAVAILABLE, TRY TO ESTABLISH A TIME WHEN YOU CAN CALL BACK.

i. This is (INTERVIEWER NAME) calling from the Fred Hutchinson Cancer Research Center. On (DATE) we made an appointment for an interview with you as part of the Hanford Thyroid Disease Study. I am calling at this time to conduct the interview.

ii. ***STATE:***

There are several things you will need to have on hand during the interview. They include your copy of the residence history, the *yellow* Calendar of Events, the *blue* Interview Booklet, a pen or pencil, and an 8 ounce measuring cup. Do you have all of them there with you now? ***If no, say:*** I'll be happy to wait while you get them. Are you ready to start now? ***Proceed.***

IF, FOR SOME REASON, THE PARTICIPANT DOES NOT HAVE THE PACKET, SAY:

I'm sorry you do not have the packet. You will need it during the interview, therefore we will need to reschedule. Let me confirm your mailing address so we can send you another packet. I will call you again in the next few days to reschedule your interview. Thank you for your patience.

END THE CALL.

As I am sure you remember, this interview is part of a study about the effects of radiation exposures from the Hanford Nuclear Reservation in the 1940's and 1950's. We are particularly interested in people who were young children during the early and mid-1940's. We hope that you can help by supplying some very important information about the childhood years of (SUBJECT), who was selected to participate in the study. The information you provide will help answer some very important questions about how the radiation from Hanford may have affected peoples' thyroid glands. Because the public was not aware of the radiation releases from Hanford, you could not have known about the possible exposure from Hanford at that time, or the possibility of side effects. Your answers to the questions will not mean that you did anything wrong, or could have prevented any exposure by doing things differently. Of course, it is important to remember that we are asking about events that occurred long ago. Local milk and produce today are not contaminated with radiation.

I hope you have had a chance to look over the materials and think about the things we will be discussing today. Before we begin the questions, there are a few things I need to mention:

- I want to assure you that all the information you give will be strictly confidential as required by public law PHS Act Section 308(d) (42 USC 242m(d)).
- You may refuse to answer any question, or terminate the interview at any time.
- Try to be as accurate and complete as possible when giving answers. Don't feel rushed, and do not hesitate to ask me to repeat a question. Our goal is to obtain the most accurate information you can give. You may not know the answers to some of the questions. Just do the best you can.
- When answering a question, please feel free to tell me everything that comes to mind, even if you aren't sure it applies to that particular question. Anything you think of may be helpful later.
- You may hear a clicking sound in the background as we talk. I'll be entering answers directly into a computer as we go through the questions. The sound is the computer keyboard.

I would now like to ask for your permission to tape record this interview. We want to have a recording of each interview for two reasons. First, the recording serves as a copy of the interview in case something happens to the computer either during or after the interview. Second, my supervisor may use the recording to evaluate my work. Remember, we are legally responsible for maintaining the confidentiality of all the information. May I have your permission to tape record the interview?

YES ..... 1 *
NO 2

* I'm starting the tape recorder.

IF SUBJECT'S BIRTHDATE IS PRIOR TO OR EQUAL TO SEPTEMBER 1945, SAY:

Let's talk for a moment about December 1944. Is there any particular event you remember from that time? It could be something related to the Holidays, a birthday or anniversary, or some other event that stands out in your mind. Think for a moment, and then tell me what you come up with.

Good.

IF SUBJECT'S BIRTHDATE IS AFTER SEPTEMBER 1945, SAY:

Let's talk for a moment about (DATE NINE MONTHS PRIOR TO SUBJECT'S BIRTH), around the time (YOU/SUBJECT'S MOTHER) became pregnant with (SUBJECT). We are interested in (YOU/SUBJECT'S MOTHER) from the time (YOU/SHE) became pregnant with (SUBJECT) until (YOU/SHE) stopped breast-feeding. Then our focus will change to (SUBJECT). Is there any other particular event you remember from that time? It could be something related to the pregnancy, a birthday or anniversary, or some other event that stands out in your mind. Think for a moment, and then tell me what you come up with. Please write these events on the calendars.

Good.

FORM APPROVED:

OMB NUMBER: 0920-0296

EXP. DATE: *(to be stamped with correct date)*

NOTE TO REVIEWERS:

A response of "unknown" from the respondent, expressed by 9, 99, or 999, depending on each question's format, is accommodated throughout the dosimetry questionnaire with some exceptions. These exceptions involve responses which name a date or provide information about changes in amounts; questions about changes require a "yes" or "no" response.

SECTION I. BACKGROUND INFORMATION *INTERVIEW START TIME:* ___ ___ : ___ ___ *A.M. / P.M.*
(QXS 100-108)

Now, let's begin the questions.

100. What is (SUBJECT'S) birthdate?

____ ____ ____ ____ ____ ____
MONTH DAY YEAR

101. Our records show that you are (SUBJECT)'s (RELATIONSHIP). Is that correct? ***If not probe for exact relationship.***

CODES:

01	***birth mother***	***08***	***grandfather***
02	***adopted mother***	***09***	***grandmother***
03	***father***	***10***	***other relative***
04	***brother***	***11***	***family friend***
05	***sister***	***12***	***other***
06	***uncle***		
07	***aunt***		

Let's turn to page 6 in the *blue* **Interview Booklet**, and talk about what (SUBJECT) ate when (HE/SHE) was an infant.

Review pages 6-7.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions?

Should we continue with the interview now?

102. Was (SUBJECT) ever nursed or breast-fed?

YES 1
NO 2
DK 9

103. How many months old was (SUBJECT) when (HE/SHE) first drank fresh milk other than breast milk?

____ ____ MONTHS OF AGE

104. ***Computer calculates month and year.***
Say: Would that be in (MONTH/YEAR)?

____ ____ / ____ ____
MONTH YEAR

Check age/date agreement with respondent
Now, please be sure that date is on your calendar, too.

YES **NO**

105. How many months old was (SUBJECT) when (HE/SHE) stopped nursing or breast-feeding?

____ ____ MONTHS OF AGE

106. ***Computer calculates month and year. Say:***
Would that be in (MONTH/YEAR)?

____ ____ ____ ____
MONTH YEAR

Check age/date agreement with respondent
Now, please write that date on your calendar, too.

SKIP TO QX. 107

107. How many months old was (SUBJECT) when (HE/SHE) first ate foods other than milk?

____ ____ MONTHS OF AGE

108. ***Computer calculates month and year. Say:***
Would that be in (MONTH/YEAR)?

____ ____ ____ ____
MONTH YEAR

Check age/date agreement with respondent
Now, please write that date on your calendar, too.

SECTION II. RESIDENCE HISTORY
(QXS 200-209)

INTERVIEWER INSTRUCTIONS:

RESIDENCE START DATE

If subject was born before December 1, 1944 *and* never breast-fed
***or* if subject stopped breast-feeding before December 1, 1944:**

RESIDENCE START DATE: December 1, 1944

If subject was born between December 1, 1944 and September 1, 1945 or born before December 1, 1944 and still breast-feeding after December 1, 1944:

RESIDENCE START DATE: December 1, 1944

If subject was born after September 1, 1945:

RESIDENCE START DATE: Date 9 months prior to birth

END DATE

If subject died before December 31, 1957:

END DATE: Date of Death

Otherwise:

END DATE: December 31, 1957

I'd now like to review the residence history information you sent to us. Please look at your copy of the Residence History Questionnaire.

For residences in our study area I will be reviewing the dates (YOU/SUBJECT'S MOTHER) and (SUBJECT) lived at each street address. For residences outside our study area, I will be reviewing the dates (YOU/SUBJECT'S MOTHER) and (SUBJECT) lived in each county and state only. Are you ready to begin?

If in study area, ask:

200. From (RESIDENCE START DATE) to (RESIDENCE END DATE) (YOU/SUBJECT'S MOTHER/SUBJECT) lived at (STREET ADDRESS) in (CITY) (STATE) which is in (COUNTY) county. Is this correct?

YES → **Go to next residence**

NO → **Get correct information, then continue**

If outside study area, ask:

201. From (COUNTY START DATE) to (COUNTY END DATE) (YOU/SUBJECT'S MOTHER/SUBJECT) lived in (COUNTY) county in (STATE). Is this correct?

YES → **Go to next residence**

NO → **Get correct information, then continue**

SECTION II.A.

The next few questions are about fresh milk and dairy products. When I say fresh milk, I mean any milk that was **not** powdered or canned. It could be processed by homogenization or pasteurization, or it could be raw.

Processed milk is usually purchased at a store. It is most often cow's milk, but can also be goat's milk.

Raw, or unprocessed milk is usually obtained from a cow or goat owned by the family, a neighbor, or friend. In some cases, raw milk could be obtained from a local dairy farm.

I will also need to know about any fresh dairy products. By fresh dairy products, I mean foods like cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. These could be made from processed or raw cow's or goat's milk. I do not want you to include aged dairy products, such as cheddar cheese, or other hard cheeses.

It will be important for you to think about any other foods eaten that contained some fresh milk or dairy products when you answer these questions.

INTERVIEWER INSTRUCTIONS:

If subject stopped breast-feeding after December 1, 1944 *or* if subject was born after December 1, 1944:

Answer SECTION II.A.:

RESIDENCE START DATE remains the same as in earlier questions.

MOTHER'S END DATE: date stopped breast-feeding *or* date of birth if not breast-fed.

Otherwise, skip to Section II.B.

INTERVIEWER CHECK: TOTAL # HTDS RESIDENCES (MOTHER) ____ ____

SECTION II.A.: ASK THESE QUESTIONS

If dates at first/next residence include any part of pregnancy with subject or breast-feeding of subject, prior to December 31, 1957.

Repeat for each HTDS residence which meets these criteria.

Otherwise, skip to SECTION II.B.

Now I have a few questions about fresh milk and fresh dairy products that (YOU/SUBJECT'S MOTHER) ate or drank while (YOU WERE/SHE WAS) (PREGNANT WITH) (AND) (BREAST-FEEDING) (SUBJECT).

202. Between (RESIDENCE START DATE) and (RESIDENCE LAST DATE/MOTHER'S END DATE), while living at (FIRST/NEXT RESIDENCE), did (YOU/SUBJECT'S MOTHER) ever eat or drink fresh milk or dairy products made from raw cow's milk?

YES 1
NO 2
DK 9

203. During that time, did (YOU/SUBJECT'S MOTHER) ever eat or drink fresh milk or dairy products made from processed cow's milk?

YES 1
NO 2
DK 9

204. During that time, did (YOU/SUBJECT'S MOTHER) ever eat or drink fresh milk or dairy products made from raw goat's milk?

YES 1
NO 2
DK 9

205. During that time, did (YOU/SUBJECT'S MOTHER) ever eat or drink fresh milk or dairy products made from processed goat's milk?

YES 1
NO 2
DK 9

Repeat SECTION II.A. for each applicable HTDS residence; then skip to SECTION II.B.

INTERVIEWER CHECK: TOTAL # HTDS RESIDENCES (SUBJECT) ____ ____

INTERVIEWER INSTRUCTIONS:

MILK START DATE:

If subject started drinking milk other than breast milk before December 1, 1944:	**MILK START DATE: December 1, 1944**
If subject never breast-fed:	**MILK START DATE: Date of Birth**
Otherwise:	**MILK START DATE: Date subject started drinking other milk**

END DATE:

If subject died before December 31, 1957:	**END DATE: Date of Death**
If last date at HTDS residence is before December 31, 1957:	**END DATE: Last date at last HTDS residence**
Otherwise:	**END DATE: December 31, 1957**

SECTION II.B.: ASK THESE QUESTIONS

If dates at first/next residence include any time during which subject drank milk other than breast milk prior to December 31, 1957;
Repeat this section for each HTDS residence which meets these criteria until END DATE.

I'd like to focus now on questions about (SUBJECT).

If questions 202-205 not asked of mother, read introduction for Section II.A.

206. Between (MILK START DATE/RESIDENCE START DATE) and (RESIDENCE LAST DATE/END DATE) did (SUBJECT) ever eat or drink fresh milk or dairy products made from raw cow's milk?
- YES 1
- NO 2
- DK 9

207. During that time, including milk provided at school, did (SUBJECT) ever eat or drink fresh milk or dairy products made from processed cow's milk?
- YES 1
- NO 2
- DK 9

208. During that time, did (SUBJECT) ever eat or drink fresh milk or dairy products made from raw goat's milk?
- YES 1
- NO 2
- DK 9

209. During that time did (SUBJECT) ever eat or drink fresh milk or dairy products made from processed goat's milk?
- YES 1
- NO 2
- DK 9

Repeat Section II.B. for each applicable HTDS residence until END DATE.

SECTION III. MILK SOURCE
(QXS 300-316)

NOTE: ASKED IF MOTHER OR SUBJECT DRANK MILK OR ATE DAIRY PRODUCTS AT HTDS STUDY COUNTY RESIDENCES AS DETERMINED IN SECTION II, RESIDENCE HISTORY

We've determined that (YOU/SUBJECT'S MOTHER) (AND/OR) (SUBJECT) ate or drank milk at residences located in the areas under study. Now I'm going to ask some specific questions about places where (YOUR/SUBJECT'S) family got different types of milk they may have drunk or eaten. I'm going to refer back to (SOME OF THE/THE) residence(s) you've told me about. As you think about a particular residence, try to recall the different stores or farms where the family got milk.

SECTION III.A.

Asked for each HTDS residence where mother and/or subject ate or drank processed, pasteurized or homogenized cow or goat's milk; it does not matter if only one or the other (subject or subject's mother) drank it for these questions.

Otherwise, skip to SECTION III.B., if appropriate.

Let's turn to page 4 of the *blue* **Interview Booklet**, and think about the brands of milk (YOUR/SUBJECT'S) family drank.

Review pages 4-5.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

These next questions will focus on the different brands of milk (YOUR/SUBJECT'S) family ate or drank. Please include milk (SUBJECT) may have gotten at school, even if you don't know the brand.

For each HTDS study residence which meets the above criteria. *Enter residence code (rc).*

300. What are the brands of milk that (YOUR/SUBJECT'S) family ate and drank while living at (FIRST/NEXT RESIDENCE).
999=DK Probe for COW or GOAT. Code: Cow=1, Goat=2.

		RECORD COW OR GOAT FOR EACH BRAND
BRAND #1	_____	COW GOAT
BRAND #2	_____	COW GOAT
BRAND #3	_____	COW GOAT
BRAND #4	_____	COW GOAT
BRAND #5	_____	COW GOAT

301. Was (BRAND) purchased at a store, a dairy or creamery, or delivered to your home? ***Record source for each brand.***

BRAND #1	DELIVERED/DAIRY/CREAMERY ___	STORE ___
BRAND #2	DELIVERED/DAIRY/CREAMERY ___	STORE ___
BRAND #3	DELIVERED/DAIRY/CREAMERY ___	STORE ___
BRAND #4	DELIVERED/DAIRY/CREAMERY ___	STORE ___
BRAND #5	DELIVERED/DAIRY/CREAMERY ___	STORE ___

302. In (RESIDENCE START DATE/CHANGE DATE) what percent of the milk was (LIST EACH BRAND NAME GIVEN)? ***If <u>not</u> equal to 100%, probe for brand name of other milk and record in QX 300.***

____ ____ ____ % BRAND #1	____ ____ ____ % BRAND #4
____ ____ ____ % BRAND #2	____ ____ ____ % BRAND #5
____ ____ ____ % BRAND #3	

303. Before (RESIDENCE LAST DATE/END DATE), did (THIS PERCENTAGE/THESE PERCENTAGES) ever change significantly?

YES

304. When did this change occur?
Probe for month/year.

____ ____ MONTH ____ ____ YEAR

NO or DK

**REPEAT FROM QX 300 FOR EACH HTDS RESIDENCE WHERE PROCESSED COW'S OR GOAT'S MILK WAS CONSUMED.
THEN SKIP TO NEXT APPLICABLE SECTION**

SECTION III.B. RAW COW'S MILK

Asked for each HTDS residence where mother and/or subject ate or drank raw cow's milk or dairy products; it does not matter if only one or the other (subject or subject's mother) drank this type of milk for these questions.

Otherwise, skip to SECTION III.C., if applicable.

Let's turn to page 2 of the *blue* **Interview Booklet**, and talk about where (YOUR/SUBJECT'S) family got milk.

Review pages 2-3.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

FOR EACH HTDS STUDY AREA RESIDENCE:

These questions are about the source of the raw cow's milk or dairy products that (YOU/SUBJECT'S MOTHER) (AND/OR) (SUBJECT) ate or drank.

You might not know the answers to some of the following questions. Just do your best. If you think there is someone else who could better answer any of these questions, please tell me and we will try to contact them also. ***(NOTE TO INTERVIEWER: RECORD NAME, ADDRESS AND TELEPHONE NUMBER IN MEMO FIELD)***

305. In (RESIDENCE START DATE/CHANGE DATE), while living at (FIRST/NEXT RESIDENCE), who owned the cows that provided most of the family's raw milk?

Family/Self 1
Neighbor 2
Relative 3
Local Dairy ***Specify*** _____ 4
Other ***Specify*** _____ 5
DK 9

306. Where were the cows kept? ***Read List:***

At (YOUR/SUBJECT'S) residence 1
Within 5 miles of (YOUR/SUBJECT'S) residence 2
More than 5 miles from (YOUR/SUBJECT'S) residence 3
(describe) _____
DK 9

307. What was the main water source for the cows kept there?

Public water supply	1	(QX 310)
Well, spring, or other underground source	2	(QX 310)
Rainwater cistern	3	(QX 308)
Pond or lake	4	(QX 309)
Stream, river, creek or irrigation canal	5	(QX 309)
Other, specify _____	6	(QX 310)
don't know	9	(QX 310)

CISTERN

308. How many days worth of rainwater did the cistern hold? ***01-98, 99=DK***

____ ____
DAYS

309. Could the cistern generally be relied on as the cow's main water source?

YES 1
NO 2
DK 9

POND/STREAM

309. Could the pond or stream generally be relied on as the cow's main water source?

YES 1
NO 2
DK 9

PUBLIC WATER/ WELL/OTHER/DK

Skip to QX 310

310. Were (OWNER'S) cows at (LOCATION) ever on pasture or fed green chop, that is, freshly cut hay or grass?

YES — **NO**

311. What percentage of the feed was pasture, green chop, or other fresh greens?

____ ____ _____ %

If 100%, Skip to QX 313

312. What percentage of the cow's feed was some type of stored hay, silage, or grain?

____ ____ _____ %

Skip to QX 313

Now I am going to ask you about any changes that might have affected the raw cow's milk your family drank. When I ask about changes in the location the cows were kept, we are concerned with changes in location of more than five miles only. When I ask about changes in water source and feed, keep in mind that we are asking for averages over a year's time. Please do not include seasonal variations.

313. While living at (RESIDENCE) and drinking milk from these cows, did the cow's location, water source, or feed ever change significantly, OR did the main source of (YOUR/SUBJECT'S) raw cow's milk ever change?

YES — **NO**

314. When did this change occur?

___ _____ _____ ___

MONTH DAY YEAR

Repeat from QX 305

Repeat QX 305 for next HTDS residence

INTERVIEWER CHECK

315. The quality of R's response was:

High Quality	**1**	**Skip to next section**
Generally Reliable	**2**	**Skip to next section**
Questionable	**3**	
Unreliable	**4**	

316. What is the main reason for the unreliable or questionable quality of this section of the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

SECTION V. MILK CONSUMPTION AND DIETARY HABITS: SUBJECT
(QXS 500-569)

In this next section I will refer to some of the answers you gave in earlier sections. With these questions I will ask you to tell me how much (SUBJECT) started eating and drinking when (HE/SHE) was a young child, and then we will discuss whether there were any significant changes in (HIS/HER) diet before (END DATE). Although amounts change gradually as a child grows, there may be times when the amounts suddenly increase or decrease.

SECTION V.A.

Asked if subject was breast-fed for 3 weeks or more during the period December 1, 1944 to December 31, 1957, while living in HTDS study area.

Let's turn to page 6 of the *blue* **Interview Booklet**, and think about when (SUBJECT) was an infant.

Review pages 6-7.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

You told me that (SUBJECT) breast-fed from (BIRTHDATE) until (DATE STOPPED BREAST-FEEDING), and that (SUBJECT) started eating or drinking milk or dairy products other than breast milk in (DATE FIRST DRANK FRESH MILK).

If time between subject birthdate and QX 103 is greater than 3 weeks, ask QX 500.

If time is 1 month or less, skip to QX 501.

500. Before the time (SUBJECT) started drinking fresh milk did (HE/SHE) ever drink powdered or canned milk?

YES 1
NO 2
DK 9

501. When (SUBJECT) started drinking fresh milk in (MILK START DATE), what percentage of the milk that (SUBJECT) was drinking was breast milk what percentage was fresh cow or goat's milk (AND WHAT PERCENTAGE WAS CANNED OR POWDERED MILK)?

____ ____ ____ % BREAST
____ ____ ____ % FRESH
____ ____ ____ % POWDERED/CANNED

NOTES TO INTERVIEWER:

For SECTIONS V.B. *through* V.E.,

MILK START DATE: Date subject began drinking fresh milk in the HTDS study area.

END DATE: The ending date at the last HTDS residence.

The questions in SECTION V.B. *through* V.E. are *not* asked for each specific residence. Answers are for continuous time periods until a change occurred. If subject stopped consuming a type of milk and started again later (or did not consume that type of milk at MILK START DATE), enter the date of change and the amount as '0'. The subsequent date of change should then be the date that milk type was again consumed.

Let's turn to page 8 in the *blue* **Interview Booklet**, and think about the milk and dairy products (SUBJECT) drank or ate.

Review Pages 8-14.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

We will be asking about each type of milk separately.

SECTION V.B.

Asked if subject ever ate or drank milk or dairy products made from raw or unprocessed cow's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from raw cow's milk. Remember, I am not interested in any milk that was canned, powdered, or processed.

502. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of raw cow's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

503. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of raw cow's milk did (SUBJECT) have per week?
99=DK Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

504. Did these amounts change significantly before (END DATE)?

YES

505. When did this change occur?
Probe for month and year.

____ ____ MONTH ____ ____ YEAR

NO

SKIP TO QX 506.

Say: I also need to know about any fresh dairy products made from raw cow's milk (SUBJECT) may have eaten or drunk, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

506. Which fresh dairy products made from raw cow's milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.C.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

507. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from raw cow's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

508. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.C.**

509. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION V.C.

Asked if subject ever ate or drank milk or dairy products made from processed cow's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from fresh processed cow's milk. Please include any milk (SUBJECT) drank while at school. I am not interested in canned or powdered milk.

510. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of processed cow's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

511. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of processed cow's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

512. Did these amounts change significantly before (END DATE)?

YES

513. When did this change occur?
Probe for month and year.

____ ____ ____ ____
MONTH YEAR

NO

SKIP TO QX 514.

Say: I also need to know about any fresh dairy products made from processed cow's milk (SUBJECT) may have eaten or drank, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

514. Which fresh dairy products made from processed cows milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.D.**

IF ANY

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

515. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from processed cow's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

516. Did this amount ever change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.D.**

YES

517. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION V.D.

Asked if subject ever ate or drank milk or dairy products made from raw or unprocessed goat's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from raw goat's milk.

518. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of raw goat's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal, and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

519. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of raw goat's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

520. Did these amounts change significantly before (END DATE)?

YES

521. When did this change occur?
Probe for month and year.

____ ____ MONTH ____ ____ YEAR

NO

SKIP TO QX 522.

Say: I also need to know about any fresh dairy products made from raw goat's milk (SUBJECT) may have eaten or drunk, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

522. Which fresh dairy products made from raw goats milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.E.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

523. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from raw goat's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

524. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.E.**

YES →

525. When did this change occur?

__ __ __ __
MONTH YEAR

→ (return to 523)

SECTION V.E.

Asked if subject ever ate or drank milk or dairy products made from processed goat's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from processed goat's milk. I am not interested in any milk that was powdered or canned.

526. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of processed goat's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

527. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of processed goat's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

528. Did these amounts change significantly before (END DATE)?

YES

529. When did this change occur?
Probe for month and year.

____ ____ ____ ____
MONTH YEAR

NO

SKIP TO QX 530.

Say: I also need to know about any fresh dairy products made from processed goat's milk (SUBJECT) may have eaten or drank, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

530. Which fresh dairy products made from processed goats milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.F.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

531. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from processed goat's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

532. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.F.**

YES →

533. When did this change occur?

__ __ __ __
MONTH YEAR

→ 531

SECTION V.F.: GREEN AND LEAFY VEGETABLES
(QXS 534-542)

Next I will be asking you about green and leafy vegetables (SUBJECT) may have eaten. I am interested *only* in fresh, locally grown green and leafy vegetables. I am not interested in any canned or frozen vegetables. By fresh vegetables, I am referring to those that were fresh and in-season locally.

Fresh vegetables could come from (YOUR/SUBJECT'S FAMILY'S) garden, from a friend, neighbor, or relative's garden, a grocery store or could be purchased directly from a farmer or at a local farmer's market or at a roadside stand. Because vegetables from a grocery store or farmer's market may have been locally grown or may have been from another area, we will ask you to estimate the percentage of vegetables that were purchased and the percentage that (YOU/SUBJECT'S FAMILY) or a neighbor grew.

Let's turn to page 15 of the *blue* **Interview Booklet**, and think about the vegetables (SUBJECT) ate.

Review pages 15-18.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

NOTES TO INTERVIEWER:

FOOD START DATE

If subject started eating foods other than milk before December 1, 1944:

FOOD START DATE: December 1, 1944

Otherwise:

FOOD START DATE: Date first ate foods other than milk (QX 112)

END DATE

If subject died before December 31, 1957:

END DATE: Date of Death

If subject moved out of HTDS area and did not return before December 31, 1957:

END DATE: Last date at last residence in HTDS area

Otherwise:

END DATE: December 31, 1957.

534. Which of these fresh green and leafy vegetables did (SUBJECT) eat from (FOOD START DATE) to (END DATE)?

IF ANY — **NONE**

NONE → **Skip to FRUITS: QX 543**

Say: I will ask questions about uncooked and cooked vegetables separately.

A serving of uncooked green and leafy vegetables is equal to a small salad bowl full.

535. In (FOOD START DATE/CHANGE DATE), how many servings of uncooked fresh green and leafy vegetables did (SUBJECT) eat per week? ***99=DK. Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 537.

536. What percentage of these uncooked vegetables were purchased and how much did (YOU/SUBJECT'S FAMILY) or a neighbor grow?

____ ____ ____ % PURCHASED
____ ____ ____ % KNOWN LOCAL

NOTE: If total is less than 75%, probe for balance.

537. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to QX 539**

538. When did this change occur?

__ __ __ __
MONTH YEAR

Say: A serving of cooked green and leafy vegetables is equal to an 8 ounce measuring cup.

539. In (FOOD START DATE/CHANGE DATE) how many servings of cooked fresh green and leafy vegetables did (SUBJECT) eat per week? ***99=DK. Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 541.

540. What percentage of these cooked vegetables were purchased and how much did (YOU/SUBJECT'S FAMILY) or a neighbor grow?

____ ____ ____ % PURCHASED
____ ____ ____ % KNOWN LOCAL

NOTE: If total is less than 75%, probe for balance.

541. Did this amount change significantly before (END DATE)?

YES — **NO**

542. When did this change occur?

__ __ __ __
MONTH YEAR

Skip to FRUITS, QX 543

SECTION IV.G.: FRESH FRUITS
(QXS 543-562)

Next I will be asking about fresh fruits (SUBJECT) may have eaten. By fresh fruits, I am referring to fruits that were fresh and in-season locally. We are interested in fruits eaten raw or cooked, but not fruits that were canned, dried, or preserved.

The fruits we are interested in fall into two general categories: those grown on trees, such as apples, peaches, and cherries, and those grown on bushes and vines, such as berries and grapes.

Let's turn to page 19 of the *blue* **Interview Booklet**, and think about the fruit (SUBJECT) ate.

Review pages 19-22.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

Let's first talk about fruit grown on trees.

543. Which of these fresh tree fruits did (SUBJECT) eat between (FOOD START DATE) and (END DATE)?

IF ANY / **NONE**

NONE → **Skip to QX 551**

Say: I will ask about raw and cooked fruits separately.

A serving of raw tree fruit is equal to a piece of fruit, except cherries for which a serving is equal to an 8 ounce measuring cup.

544. In (FOOD START DATE/CHANGE DATE), how many servings of raw tree fruit did (SUBJECT) eat per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 546.

545. Was the fruit peeled or washed before (SUBJECT) ate it *READ LIST*

NEVER 1
SOMETIMES 2
ALWAYS 3
DK 9

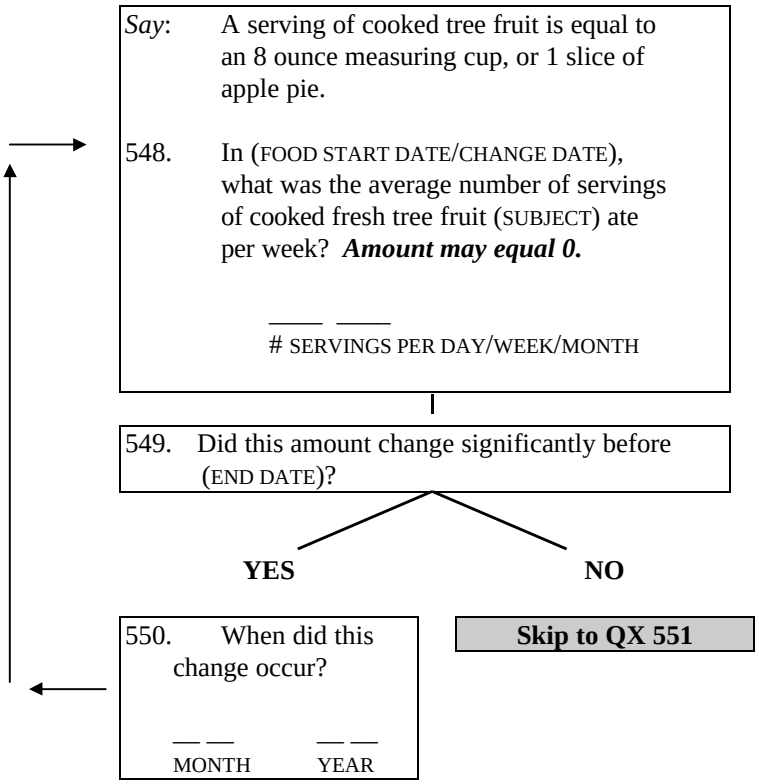
546. Did this amount change significantly before (END DATE)?

YES / **NO**

NO → **Skip to QX 548**

547. When did this change occur?

__ __ __ __
MONTH YEAR


Say: A serving of cooked tree fruit is equal to an 8 ounce measuring cup, or 1 slice of apple pie.
548. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of cooked fresh tree fruit (SUBJECT) ate per week? ***Amount may equal 0.***
____ ____
SERVINGS PER DAY/WEEK/MONTH
549. Did this amount change significantly before (END DATE)?
YES
NO
550. When did this change occur?
__ __ __ __
MONTH YEAR
Skip to QX 551

The next questions are about fruits grown on vines or bushes, such as berries and grapes.

551. Which of these fresh bush or vine fruits did (SUBJECT) eat between (FOOD START DATE) and (END DATE)?

IF ANY / **NONE**

NONE → **Skip to QX 559**

Say: I will ask about raw and cooked fruits separately.

A serving of raw vine or bush fruit is equal to an 8 ounce measuring cup.

552. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of raw vine or bush fruit (SUBJECT) ate per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 554.

553. Was the fruit peeled or washed before (SUBJECT) ate it ***READ LIST***

NEVER.....1
SOMETIMES.....2
ALWAYS.....3
DON'T KNOW.....9

554. Did this amount change significantly before (END DATE)?

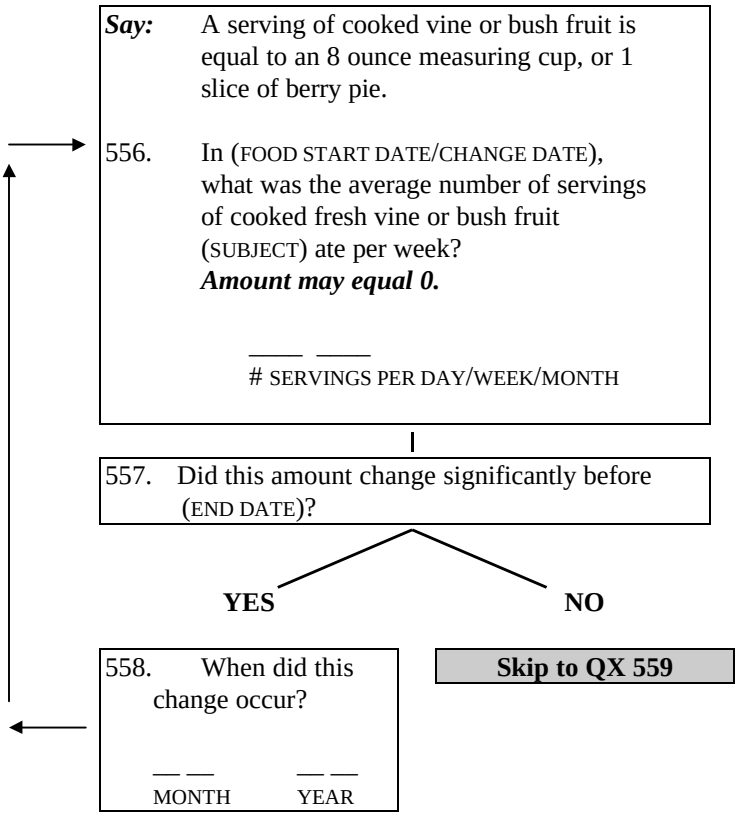
YES / **NO**

NO → **Skip to QX 556**

555. When did this change occur?

__ __ __ __
MONTH YEAR

→ QX 552


Say: A serving of cooked vine or bush fruit is equal to an 8 ounce measuring cup, or 1 slice of berry pie.
556. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of cooked fresh vine or bush fruit (SUBJECT) ate per week?
Amount may equal 0.
____ ____
SERVINGS PER DAY/WEEK/MONTH
557. Did this amount change significantly before (END DATE)?
YES
NO
558. When did this change occur?
__ __ __ __
MONTH YEAR
Skip to QX 559

The next questions are about fresh fruit juices. These juices could have been freshly pressed or squeezed from in-season tree, vine or bush fruits such as apples or grapes. I am interested in fresh juice only; not canned or preserved juices.

559. From (FOOD START DATE) to (END DATE), did (SUBJECT) ever drink fresh juice made from in-season fruits?

YES **NO**

Skip to QX 563

Say: A serving of fresh fruit juice is equal to an 8 ounce glass.

560. In (FOOD START DATE/CHANGE DATE), what was the average number of 8 ounce glasses of fresh fruit juice (SUBJECT) drank per week? ***Amount may equal 0.***

____ ____
GLASSES PER DAY/WEEK/MONTH

561. Did this amount change significantly before (END DATE)?

YES **NO**

Skip to QX 563

562. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION IV.H.: EGG CONSUMPTION
(QXS 563-566)

I will now ask about eggs (SUBJECT) ate.

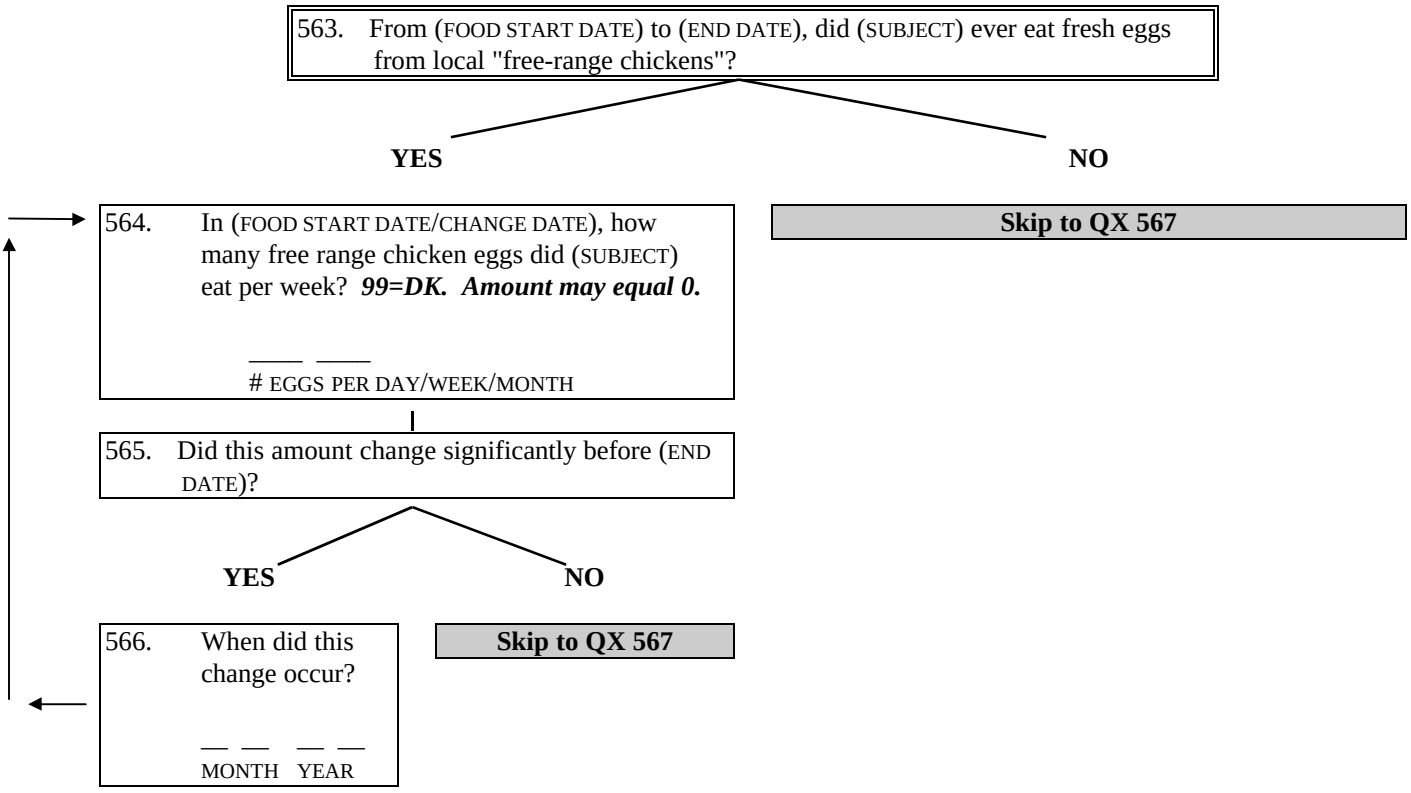
I am only interested in fresh eggs from local "free-range" chickens, that is, chickens who were allowed to be outside. I am not interested in any eggs from chickens that were always in a covered chicken coop, or any eggs purchased at the market or store.

Let's turn to page 23 of the *blue* **Interview Booklet**, and think about free-range chicken eggs.

Review pages 23-24.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

I will need you to consider the eggs from local free-range chickens eaten, even as ingredients in other foods.



INTERVIEWER CHECK

567. The quality of R's response was:

High Quality	**1**	**Skip to next section**
Generally Reliable	**2**	**Skip to next section**
Questionable	**3**	
Unreliable	**4**	

568. What is the main reason for the unreliable or questionable quality of this section of the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

569. How often was explanation text repeated?

Very often	**1**
Often	**2**
Not often	**3**
Not applicable	**4**

SECTION V. MILK CONSUMPTION AND DIETARY HABITS: SUBJECT
(QXS 500-569)

In this next section I will refer to some of the answers you gave in earlier sections. With these questions I will ask you to tell me how much (SUBJECT) started eating and drinking when (HE/SHE) was a young child, and then we will discuss whether there were any significant changes in (HIS/HER) diet before (END DATE). Although amounts change gradually as a child grows, there may be times when the amounts suddenly increase or decrease.

SECTION V.A.

Asked if subject was breast-fed for 3 weeks or more during the period December 1, 1944 to December 31, 1957, while living in HTDS study area.

Let's turn to page 6 of the *blue* **Interview Booklet**, and think about when (SUBJECT) was an infant.

Review pages 6-7.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

You told me that (SUBJECT) breast-fed from (BIRTHDATE) until (DATE STOPPED BREAST-FEEDING), and that (SUBJECT) started eating or drinking milk or dairy products other than breast milk in (DATE FIRST DRANK FRESH MILK).

If time between subject birthdate and QX 103 is greater than 3 weeks, ask QX 500.

If time is 1 month or less, skip to QX 501.

500. Before the time (SUBJECT) started drinking fresh milk did (HE/SHE) ever drink powdered or canned milk?

YES 1
NO 2
DK 9

501. When (SUBJECT) started drinking fresh milk in (MILK START DATE), what percentage of the milk that (SUBJECT) was drinking was breast milk what percentage was fresh cow or goat's milk (AND WHAT PERCENTAGE WAS CANNED OR POWDERED MILK)?

____ ____ ____ % BREAST
____ ____ ____ % FRESH
____ ____ ____ % POWDERED/CANNED

NOTES TO INTERVIEWER:

For SECTIONS V.B. *through* V.E.,

MILK START DATE: Date subject began drinking fresh milk in the HTDS study area.

END DATE: The ending date at the last HTDS residence.

The questions in SECTION V.B. *through* V.E. are *not* asked for each specific residence. Answers are for continuous time periods until a change occurred. If subject stopped consuming a type of milk and started again later (or did not consume that type of milk at MILK START DATE), enter the date of change and the amount as '0'. The subsequent date of change should then be the date that milk type was again consumed.

Let's turn to page 8 in the *blue* **Interview Booklet**, and think about the milk and dairy products (SUBJECT) drank or ate.

Review Pages 8-14.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

We will be asking about each type of milk separately.

SECTION V.B.

Asked if subject ever ate or drank milk or dairy products made from raw or unprocessed cow's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from raw cow's milk. Remember, I am not interested in any milk that was canned, powdered, or processed.

502. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of raw cow's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

503. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of raw cow's milk did (SUBJECT) have per week?
99=DK Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

504. Did these amounts change significantly before (END DATE)?

YES

505. When did this change occur?
Probe for month and year.

____ ____ MONTH ____ ____ YEAR

NO

SKIP TO QX 506.

Say: I also need to know about any fresh dairy products made from raw cow's milk (SUBJECT) may have eaten or drunk, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

506. Which fresh dairy products made from raw cow's milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.C.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

507. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from raw cow's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

508. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.C.**

YES →

509. When did this change occur?

__ __ __ __
MONTH YEAR

→ back to 507

SECTION V.C.

Asked if subject ever ate or drank milk or dairy products made from processed cow's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from fresh processed cow's milk. Please include any milk (SUBJECT) drank while at school. I am not interested in canned or powdered milk.

510. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of processed cow's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

511. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of processed cow's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

512. Did these amounts change significantly before (END DATE)?

YES

513. When did this change occur?
Probe for month and year.

____ ____ ____ ____
MONTH YEAR

NO

SKIP TO QX 514.

Say: I also need to know about any fresh dairy products made from processed cow's milk (SUBJECT) may have eaten or drank, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

514. Which fresh dairy products made from processed cows milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.D.**

IF ANY

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

515. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from processed cow's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

516. Did this amount ever change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.D.**

YES

517. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION V.D.

Asked if subject ever ate or drank milk or dairy products made from raw or unprocessed goat's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from raw goat's milk.

518. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of raw goat's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal, and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

519. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of raw goat's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

520. Did these amounts change significantly before (END DATE)?

YES

521. When did this change occur?
Probe for month and year.

____ ____ MONTH ____ ____ YEAR

NO

SKIP TO QX 522.

Say: I also need to know about any fresh dairy products made from raw goat's milk (SUBJECT) may have eaten or drunk, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

522. Which fresh dairy products made from raw goats milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.E.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

523. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from raw goat's milk did (SUBJECT) have per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

524. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.E.**

YES →

525. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION V.E.

Asked if subject ever ate or drank milk or dairy products made from processed goat's milk at HTDS residences between (MILK START DATE) and (END DATE).

You said that (SUBJECT) ate or drank products made from processed goat's milk. I am not interested in any milk that was powdered or canned.

526. In (MILK START DATE/CHANGE DATE), how many 8 ounce glasses (OR BOTTLES) of processed goat's milk did (SUBJECT) drink per week?
99=DK Amount may equal 0.

____ ____
GLASSES PER DAY/WEEK/MONTH

Say: Now consider milk (SUBJECT) had on cereal and fruit, or in cooked foods such as casseroles, soups, sauces and desserts, or in coffee or tea.

527. In (MILK START DATE/CHANGE DATE), how many 8 ounce servings of processed goat's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

528. Did these amounts change significantly before (END DATE)?

YES

529. When did this change occur?
Probe for month and year.

____ ____ ____ ____
MONTH YEAR

NO

SKIP TO QX 530.

Say: I also need to know about any fresh dairy products made from processed goat's milk (SUBJECT) may have eaten or drank, such as cream, butter, buttermilk, cottage cheese, yogurt, and ice cream. Many cooked foods, such as casseroles and desserts, also contain fresh dairy products.

Please do not include aged dairy products, such as cheddar cheese or other hard cheeses.

530. Which fresh dairy products made from processed goats milk did (SUBJECT) eat or drink between (MILK START DATE) and (END DATE)?

IF ANY — **NONE**

NONE → **SKIP TO SECTION V.F.**

Say: A serving of butter is equal to 1-1/2 teaspoons, and a serving of any other dairy product is equal to an 8 ounce measuring cup.

531. In (MILK START DATE/CHANGE DATE), how many servings of fresh dairy products made from processed goat's milk did (SUBJECT) have per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

532. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to Section V.F.**

YES → 533. When did this change occur?

__ __ __ __
MONTH YEAR

→ back to 531

SECTION V.F.: GREEN AND LEAFY VEGETABLES
(QXS 534-542)

Next I will be asking you about green and leafy vegetables (SUBJECT) may have eaten. I am interested *only* in fresh, locally grown green and leafy vegetables. I am not interested in any canned or frozen vegetables. By fresh vegetables, I am referring to those that were fresh and in-season locally.

Fresh vegetables could come from (YOUR/SUBJECT'S FAMILY'S) garden, from a friend, neighbor, or relative's garden, a grocery store or could be purchased directly from a farmer or at a local farmer's market or at a roadside stand. Because vegetables from a grocery store or farmer's market may have been locally grown or may have been from another area, we will ask you to estimate the percentage of vegetables that were purchased and the percentage that (YOU/SUBJECT'S FAMILY) or a neighbor grew.

Let's turn to page 15 of the *blue* **Interview Booklet**, and think about the vegetables (SUBJECT) ate.

Review pages 15-18.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

NOTES TO INTERVIEWER:

FOOD START DATE

If subject started eating foods other than milk before December 1, 1944:

FOOD START DATE: December 1, 1944

Otherwise:

FOOD START DATE: Date first ate foods other than milk (QX 112)

END DATE

If subject died before December 31, 1957:

END DATE: Date of Death

If subject moved out of HTDS area and did not return before December 31, 1957:

END DATE: Last date at last residence in HTDS area

Otherwise:

END DATE: December 31, 1957.

534. Which of these fresh green and leafy vegetables did (SUBJECT) eat from (FOOD START DATE) to (END DATE)?

IF ANY — **NONE**

NONE → **Skip to FRUITS: QX 543**

Say: I will ask questions about uncooked and cooked vegetables separately.

A serving of uncooked green and leafy vegetables is equal to a small salad bowl full.

535. In (FOOD START DATE/CHANGE DATE), how many servings of uncooked fresh green and leafy vegetables did (SUBJECT) eat per week? ***99=DK. Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 537.

536. What percentage of these uncooked vegetables were purchased and how much did (YOU/SUBJECT'S FAMILY) or a neighbor grow?

____ ____ ____ % PURCHASED
____ ____ ____ % KNOWN LOCAL

NOTE: If total is less than 75%, probe for balance.

537. Did this amount change significantly before (END DATE)?

YES — **NO**

NO → **Skip to QX 539**

538. When did this change occur?

__ __ __ __
MONTH YEAR

Say: A serving of cooked green and leafy vegetables is equal to an 8 ounce measuring cup.

539. In (FOOD START DATE/CHANGE DATE) how many servings of cooked fresh green and leafy vegetables did (SUBJECT) eat per week? ***99=DK. Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 541.

540. What percentage of these cooked vegetables were purchased and how much did (YOU/SUBJECT'S FAMILY) or a neighbor grow?

____ ____ ____ % PURCHASED
____ ____ ____ % KNOWN LOCAL

NOTE: If total is less than 75%, probe for balance.

541. Did this amount change significantly before (END DATE)?

YES — **NO**

542. When did this change occur?

__ __ __ __
MONTH YEAR

Skip to FRUITS, QX 543

SECTION IV.G.: FRESH FRUITS
(QXS 543-562)

Next I will be asking about fresh fruits (SUBJECT) may have eaten. By fresh fruits, I am referring to fruits that were fresh and in-season locally. We are interested in fruits eaten raw or cooked, but not fruits that were canned, dried, or preserved.

The fruits we are interested in fall into two general categories: those grown on trees, such as apples, peaches, and cherries, and those grown on bushes and vines, such as berries and grapes.

Let's turn to page 19 of the *blue* **Interview Booklet**, and think about the fruit (SUBJECT) ate.

Review pages 19-22.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

Let's first talk about fruit grown on trees.

543. Which of these fresh tree fruits did (SUBJECT) eat between (FOOD START DATE) and (END DATE)?

IF ANY / **NONE**

NONE → **Skip to QX 551**

Say: I will ask about raw and cooked fruits separately.

A serving of raw tree fruit is equal to a piece of fruit, except cherries for which a serving is equal to an 8 ounce measuring cup.

544. In (FOOD START DATE/CHANGE DATE), how many servings of raw tree fruit did (SUBJECT) eat per week?
Amount may equal 0.

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 546.

545. Was the fruit peeled or washed before (SUBJECT) ate it *READ LIST*

NEVER.....1
SOMETIMES.....2
ALWAYS.....3
DK.....9

546. Did this amount change significantly before (END DATE)?

YES / **NO**

NO → **Skip to QX 548**

547. When did this change occur?

__ __ __ __
MONTH YEAR

Say: A serving of cooked tree fruit is equal to an 8 ounce measuring cup, or 1 slice of apple pie.

548. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of cooked fresh tree fruit (SUBJECT) ate per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

549. Did this amount change significantly before (END DATE)?

YES **NO**

550. When did this change occur?

__ __ __ __
MONTH YEAR

Skip to QX 551

The next questions are about fruits grown on vines or bushes, such as berries and grapes.

551. Which of these fresh bush or vine fruits did (SUBJECT) eat between (FOOD START DATE) and (END DATE)?

IF ANY / **NONE**

NONE → **Skip to QX 559**

Say: I will ask about raw and cooked fruits separately.

A serving of raw vine or bush fruit is equal to an 8 ounce measuring cup.

552. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of raw vine or bush fruit (SUBJECT) ate per week? ***Amount may equal 0.***

____ ____
SERVINGS PER DAY/WEEK/MONTH

If 0, skip to QX 554.

553. Was the fruit peeled or washed before (SUBJECT) ate it ***READ LIST***

NEVER.....1
SOMETIMES.....2
ALWAYS.....3
DON'T KNOW.....9

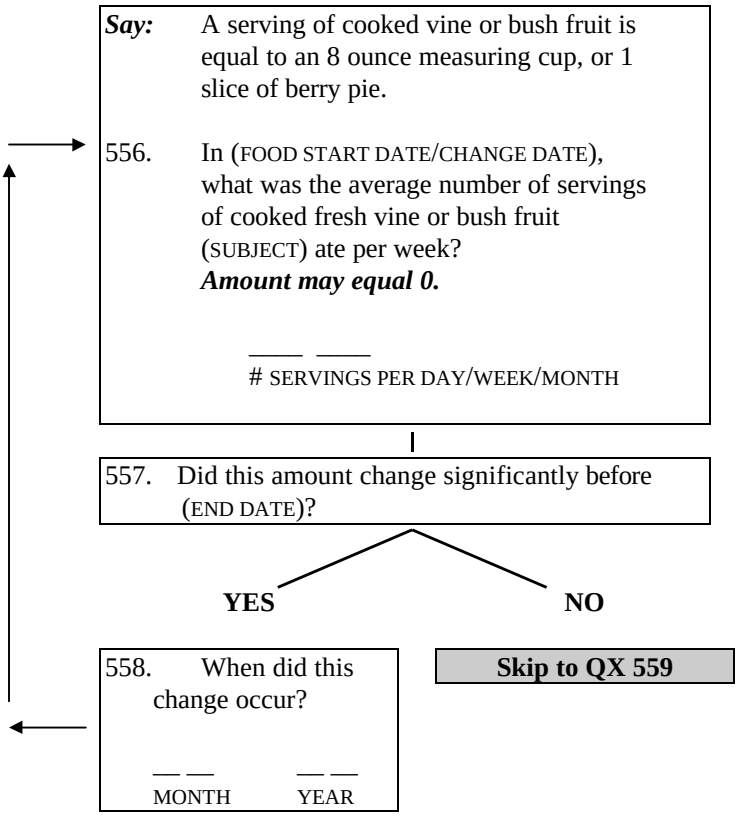
554. Did this amount change significantly before (END DATE)?

YES / **NO**

NO → **Skip to QX 556**

555. When did this change occur?

__ __ __ __
MONTH YEAR


Say: A serving of cooked vine or bush fruit is equal to an 8 ounce measuring cup, or 1 slice of berry pie.
556. In (FOOD START DATE/CHANGE DATE), what was the average number of servings of cooked fresh vine or bush fruit (SUBJECT) ate per week?
Amount may equal 0.
____ ____
SERVINGS PER DAY/WEEK/MONTH
557. Did this amount change significantly before (END DATE)?
YES
NO
558. When did this change occur?
__ __ __ __
MONTH YEAR
Skip to QX 559

The next questions are about fresh fruit juices. These juices could have been freshly pressed or squeezed from in-season tree, vine or bush fruits such as apples or grapes. I am interested in fresh juice only; not canned or preserved juices.

559. From (FOOD START DATE) to (END DATE), did (SUBJECT) ever drink fresh juice made from in-season fruits?

YES **NO**

Skip to QX 563

Say: A serving of fresh fruit juice is equal to an 8 ounce glass.

560. In (FOOD START DATE/CHANGE DATE), what was the average number of 8 ounce glasses of fresh fruit juice (SUBJECT) drank per week? ***Amount may equal 0.***

____ ____
GLASSES PER DAY/WEEK/MONTH

561. Did this amount change significantly before (END DATE)?

YES **NO**

Skip to QX 563

562. When did this change occur?

__ __ __ __
MONTH YEAR

SECTION IV.H.: EGG CONSUMPTION
(QXS 563-566)

I will now ask about eggs (SUBJECT) ate.

I am only interested in fresh eggs from local "free-range" chickens, that is, chickens who were allowed to be outside. I am not interested in any eggs from chickens that were always in a covered chicken coop, or any eggs purchased at the market or store.

Let's turn to page 23 of the *blue* **Interview Booklet**, and think about free-range chicken eggs.

Review pages 23-24.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

I will need you to consider the eggs from local free-range chickens eaten, even as ingredients in other foods.

563. From (FOOD START DATE) to (END DATE), did (SUBJECT) ever eat fresh eggs from local "free-range chickens"?

YES — **NO** → **Skip to QX 567**

564. In (FOOD START DATE/CHANGE DATE), how many free range chicken eggs did (SUBJECT) eat per week? ***99=DK. Amount may equal 0.***

____ ____
EGGS PER DAY/WEEK/MONTH

565. Did this amount change significantly before (END DATE)?

YES — **NO** → **Skip to QX 567**

566. When did this change occur?

__ __ __ __
MONTH YEAR

INTERVIEWER CHECK

567. The quality of R's response was:

High Quality	**1**	**Skip to next section**
Generally Reliable	**2**	**Skip to next section**
Questionable	**3**	
Unreliable	**4**	

568. What is the main reason for the unreliable or questionable quality of this section of the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

569. How often was explanation text repeated?

Very often	**1**
Often	**2**
Not often	**3**
Not applicable	**4**

SECTION VI. MEDICAL HISTORY: MOTHER
(QXS 600-661)

Now I would like to ask you some questions about (YOUR/SUBJECT'S MOTHER'S) health beginning in (DATE 9 MONTHS PRIOR TO SUBJECT'S BIRTH) when (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT). It is important for us to know about several different types of medical procedures that may have been performed. The first group of questions are about radiologic procedures such as a chest x-ray.

Let's turn to page 25 of the *blue* **Interview Booklet**, and think about some medical tests and procedures (YOU/SUBJECT'S MOTHER) may have had while pregnant.

Review pages 25-26.

Please take your time to think about this topic. Do you have any thoughts you would like share, or any questions? ***(pause)*** Should we continue with the interview now?

RADIOLOGIC PROCEDURES

600. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), were any x-rays taken of (YOUR/HER) **pelvis (also called a fetal x-ray)**?

YES — **NO**

601. On how many different occasions were x-rays taken of the pelvis (or fetal x-rays)?

____ ____
OF OCCASIONS

602. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), were any x-rays taken of (YOUR/HER) **Chest or Upper Back**?

YES — **NO**

603. On how many different occasions were x-rays taken of the chest or upper back?

____ ____
OF OCCASIONS

604. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), were any x-rays taken of (YOUR/HER) **mid- or lower-back**?

YES — **NO**

605. On how many different occasions were x-rays taken of the mid- or lower-back?

____ ____
OF OCCASIONS

Skip to QX 606

FLUOROSCOPIES

Now I will be asking you questions about any fluoroscopies that may have been taken while (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT). A fluoroscopy is a type of x-ray in which the doctor may be standing next to the patient observing certain parts of the body on a fluorescent screen like a TV set. The doctor can see how the various parts of the body work by watching the screen. No pictures are taken. A fluoroscopy may be performed for a variety of reasons. In many cases such as Barium Enemas, Upper G.I.'s and I.V.P.'s (intravenous pyelogram) a dye may be swallowed or injected into a vein, then a certain part of the body is viewed on a fluoroscope.

For the next group of questions, I will be referring to the upper body anatomy chart on the last page of the *blue* Interview Booklet. When I say "upper body", I am referring to the shaded portion of this diagram.

606. When (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), did (YOU/SHE) ever have a **Barium Enema**?

YES — **NO**

607. On how many different occasions did (YOU/SHE) have a barium enema?

____ _____ # OCCASIONS

608. When (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), did (YOU/SHE) ever have an **Upper G.I.**?

YES — **NO**

609. On how many different occasions did (YOU/SHE) have an Upper G.I.?

____ ____ # OCCASIONS

610. When (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), did (YOU/SHE) ever have an **I.V.P. (intravenous pyelogram)**?

YES — **NO**

611. On how many different occasions did (YOU/SHE) have an IVP?

____ ____ # OCCASIONS

Skip to FLUOROSCOPIES, QX 612

612. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), were any other fluoroscopies performed on (YOUR/HER) upper body?
(Specify part of upper body)

YES

613. On how many different occasions did (YOU/SHE) have a fluoroscopy of another part of the upper body?

____ ____ # OCCASIONS

NO

Skip to THYROID SCANS, QX. 614

THYROID SCANS AND OTHER DIAGNOSTIC NUCLEAR MEDICINE

Now I would like to ask you questions about any thyroid scans or other diagnostic nuclear medicine procedures (YOU/SUBJECT'S MOTHER) may have had during (YOUR/HER) pregnancy.

614. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), did (YOU/SHE) ever have a thyroid scan?

YES

615. On how many different occasions did (YOU/SUBJECT'S MOTHER) have thyroid scans during this pregnancy?

____ ____
OCCASIONS

NO

616. While (YOU WERE/SUBJECT'S MOTHER WAS) pregnant with (SUBJECT), did (YOU/SHE) ever take a radioactive substance by mouth or have a radioactive substance injected into a vein to diagnose a medical problem?

YES

617. On how many occasions during this pregnancy was this diagnostic procedure performed?

____ ____
OCCASIONS

NO

Skip to THYROID PROBLEMS, QX 618

THYROID PROBLEMS: MOTHER

The next group of questions I am going to ask are about thyroid problems (YOU/SUBJECT'S MOTHER) may have had during (YOUR/HER) pregnancy with (SUBJECT). These could be thyroid diseases diagnosed during the pregnancy or thyroid diseases diagnosed before the pregnancy that were being treated during the pregnancy. I will be asking what type of problem it was, and the type of treatment given.

Let's turn to page 27 of the *blue* **Interview Booklet**, and think about any thyroid problems (YOU/SUBJECT'S MOTHER) may have had during this time.

Review pages 27-28.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

618. Either before or during (YOUR/SUBJECT'S MOTHER'S) pregnancy with (SUBJECT), did a doctor ever tell (YOU/HER) that (YOU/SHE) had **Graves' Disease or hyperthyroidism, that is, an over-active thyroid**?

YES — **NO**

NO → **Skip to QX 625, Hypothyroidism**

Please tell me if (YOU/SUBJECT'S MOTHER) had any of the following treatments for Graves' Disease or Hyperthyroidism during (YOUR/HER) pregnancy.

619. Did (YOU/SUBJECT'S MOTHER) ever take **medication** for this condition during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

620. What kind of medication did (YOU/SHE) take for this condition? ***Record Verbatim***

621. Did (YOU/SUBJECT'S MOTHER) ever have **radiation treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

622. What kind of radiation treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

623. Did (YOU/SUBJECT'S MOTHER) ever have any **other type of treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

624. What other type of treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

NO → **Skip to QX 625.**

625. Either before or during (YOUR/SUBJECT'S MOTHER'S) pregnancy with (SUBJECT), did a doctor ever tell (YOU/HER) that (YOU/SHE) had **Hypothyroidism, that is, an under-active thyroid**?

YES

Please tell me if (YOU/SUBJECT'S MOTHER) had any of the following treatments for Hypothyroidism during (YOUR/HER) pregnancy.

626. Did (YOU/SUBJECT'S MOTHER) ever take **medication** for this condition during (YOUR/HER) pregnancy with (SUBJECT)?

YES

627. What kind of medication did (YOU/SHE) take for this condition?
Record Verbatim

NO

628. Did (YOU/SUBJECT'S MOTHER) ever have **radiation treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES

629. What kind of radiation treatment did (YOU/SHE) have for this condition?
Record Verbatim

NO

630. Did (YOU/SUBJECT'S MOTHER) ever have any **other type of treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES

631. What other type of treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

NO

Skip to QX 632.

NO

Skip to QX 632,
Malignant Thyroid Tumor or Lump

632. Either before or during (YOUR/SUBJECT'S MOTHER'S) pregnancy with (SUBJECT), did a doctor ever tell (YOU/HER) that (YOU/SHE) had a **Malignant Thyroid Tumor or Lump**?

YES — **NO**

NO → **Skip to QX 639, Benign Thyroid Tumor or Lump**

Please tell me if (YOU/SUBJECT'S MOTHER) had any of the following treatments for a Malignant Thyroid Tumor or Lump during (YOUR/HER) pregnancy.

633. Did (YOU/SUBJECT'S MOTHER) ever take **medication** for this condition during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

634. What kind of medication did (YOU/SHE) take for this condition? ***Record Verbatim***

635. Did (YOU/SUBJECT'S MOTHER) ever have **radiation treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

636. What kind of radiation treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

637. Did (YOU/SUBJECT'S MOTHER) ever have any **other type of treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

638. What other type of treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

NO → **Skip to QX 639.**

639. Either before or during (YOUR/SUBJECT'S MOTHER'S) pregnancy with (SUBJECT), did a doctor ever tell (YOU/HER) that (YOU/SHE) had a **Benign Thyroid Tumor or Lump**?

YES — **NO**

NO → **Skip to QX 646, Goiter**

Please tell me if (YOU/SUBJECT'S MOTHER) had any of the following treatments for a Benign Thyroid Tumor or Lump during (YOUR/HER) pregnancy.

640. Did (YOU/SUBJECT'S MOTHER) ever take **medication** for this condition during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

641. What kind of medication did (YOU/SHE) take for this condition?
Record Verbatim

642. Did (YOU/SUBJECT'S MOTHER) ever have **radiation treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

643. What kind of radiation treatment did (YOU/SHE) have for this condition?
Record Verbatim

644. Did (YOU/SUBJECT'S MOTHER) ever have any **other type of treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

645. What other type of treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

NO → **Skip to QX 646.**

646. Either before or during (YOUR/SUBJECT'S MOTHER'S) pregnancy with (SUBJECT), did a doctor ever tell (YOU/HER) that (YOU/SHE) had **Goiter**?

YES — **NO**

NO → **Skip to QX 653**

Please tell me if (YOU/SUBJECT'S MOTHER) had any of the following treatments for Goiter during (YOUR/HER) pregnancy.

647. Did (YOU/SUBJECT'S MOTHER) ever take **medication** for this condition during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

648. What kind of medication did (YOU/SHE) take for this condition?
Record Verbatim

649. Did (YOU/SUBJECT'S MOTHER) ever have **radiation treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

650. What kind of radiation treatment did (YOU/SHE) have for this condition?
Record Verbatim

651. Did (YOU/SUBJECT'S MOTHER) ever have any **other type of treatment** for (CONDITION) during (YOUR/HER) pregnancy with (SUBJECT)?

YES — **NO**

YES →

652. What other type of treatment did (YOU/SHE) have for this condition? ***Record Verbatim***

NO → **Skip to QX 653.**

653. Other than for the reasons we've just talked about, did (YOU/SUBJECT'S MOTHER) take any thyroid medication during (YOUR/HER) pregnancy with (SUBJECT)?

YES

Skip to QX 656

654. What kind of medication did (YOU/SHE) take? ***Record Verbatim***

655. Why did (YOU/SHE) take this medication? ***Record Verbatim***

NO

656. Other than for the reasons we've just talked about, did (YOU/SUBJECT'S MOTHER) have any thyroid radiation treatment during (your/her) pregnancy with (SUBJECT)?

YES

NO

Skip to Interviewer Check, QX 659

657. Why did (YOU/SHE) have thyroid radiation treatment? ***Record Verbatim***

658. On how many different occasions during (YOUR/HER) pregnancy did (YOU/SHE) have thyroid radiation treatment? ***99=DK***

____ ____
OCCASIONS

INTERVIEWER CHECK

659. The quality of R's response was:

High Quality	**1**	**Skip to next section**
Generally Reliable	**2**	**Skip to next section**
Questionable	**3**	
Unreliable	**4**	

660. What is the main reason for the unreliable or questionable quality of this section of the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

SECTION VII. MEDICAL HISTORY: SUBJECT
(QXS 700-881)

Now I would like to find out about (SUBJECT'S) medical history from birth to age 15.

DIAGNOSTIC X-RAYS

The first group of questions I am going to ask are about x-ray procedures done to diagnose a problem or condition of the upper body. I am now referring to x-rays taken to diagnose broken bones or other conditions, *not including* dental

x-rays. Please look at the last page of the *blue* Interview Booklet. You will see a picture with a shaded portion I will refer to as the upper body. When answering these questions, please remember that I am only interested in procedures done in this area of the body. These procedures could include any x-rays taken for screening purposes, such as chest x-rays to detect tuberculosis.

Now let's turn to page 29 of the *blue* **Interview Booklet**, and think about any diagnostic x-rays (SUBJECT) may have had before age 15.

Review pages 29-30.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

700. Before age 15, did (SUBJECT) ever have any diagnostic x-rays taken of (HIS/HER) **Head,** including x-rays for oral surgery or orthodontic work, but *not* routine dental visits?

YES — **NO**

701. How old was (SUBJECT) when (HE/SHE) had the first x-ray of (HIS/HER) head?
Record months or years for age

____ ____ MONTHS/YEARS

702. On how many occasions were x-rays taken of (HIS/HER) head?

____ ____ # OCCASIONS

703. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

704. Before age 15, did (SUBJECT) ever have any diagnostic x-rays taken of (HIS/HER) **Neck**?

YES — **NO**

705. How old was (SUBJECT) when (HE/SHE) had the first x-ray of (HIS/HER) neck?
Record months or years for age

____ ____ MONTHS/YEARS

706. On how many occasions were x-rays taken of (HIS/HER) neck?

____ ____ # OCCASIONS

707. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

Skip to QX 708, Chest or Upper Back

708. Before age 15, did (SUBJECT) ever have any diagnostic x-rays taken of (HIS/HER) **Chest or Upper Back**?

YES — **NO**

709. How old was (SUBJECT) when (HE/SHE) had the first x-ray of (HIS/HER) chest or upper back? ***Record months or years for age***

____ ____ MONTHS/YEARS

710. On how many occasions were x-rays taken of (HIS/HER) chest or upper back?

____ ____ # OCCASIONS

711. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

712. Before age 15, did (SUBJECT) ever have any diagnostic x-rays taken of **any other part of (HIS/HER) upper body**?

YES — **NO**

713. On what part of the upper body was the x-ray taken? ***Record Verbatim***

714. How old was (SUBJECT) when (HE/SHE) had the first x-ray of (HIS/HER) (UPPER BODY PART)?
Record months or years for age

____ ____ MONTHS/YEARS

715. On how many occasions were x-rays taken of (HIS/HER) (UPPER BODY PART)?

____ ____ # OCCASIONS

716. Was a lead apron usually placed over the neck area?

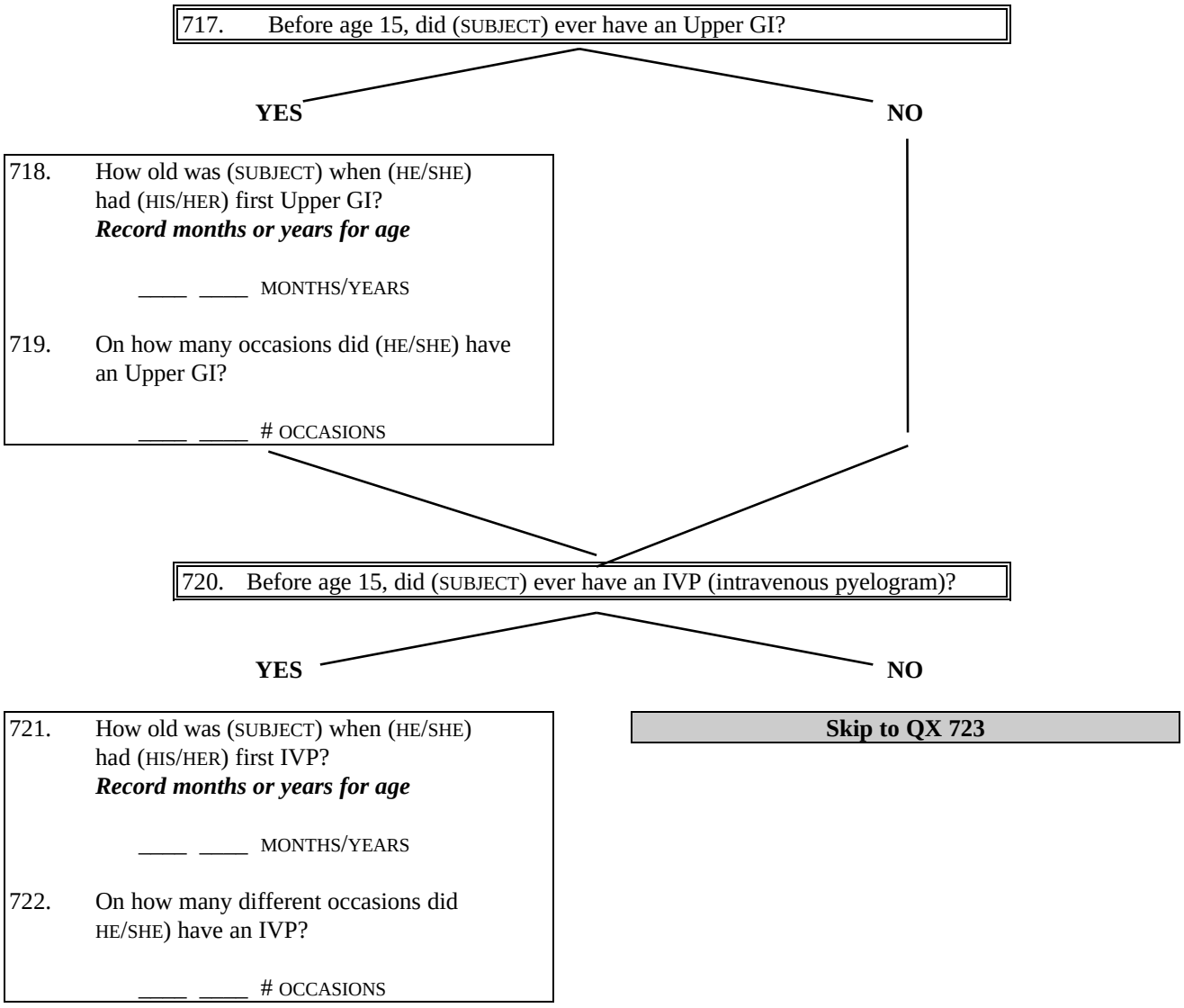
YES 1
NO 2
DK 9

Skip to QX 717, Upper G.I.

FLUOROSCOPIES

Now I will be asking you questions about any fluoroscopies that (subject) may have had before age 15. A fluoroscopy is a type of x-ray in which the doctor may be standing next to the patient observing certain parts of the body on a fluorescent screen like a TV set. The doctor can see how the various parts of the body work by watching the screen. No pictures are taken. In many cases such as Upper G.I.'s and I.V.P.'s (intravenous pyelogram) a dye may be swallowed or injected into a vein, then a certain part of the body is viewed on a fluoroscope.

For the next group of questions, I will be referring to the upper body anatomy chart on the last page of the *blue* Interview Booklet. When I say "upper body", I am referring to the shaded portion of this diagram.



723. Before age 15, did (SUBJECT) ever have any other fluoroscopies performed on (HIS/HER) upper body? ***Specify body part***

YES **NO**

724. How old was (SUBJECT) when (HE/SHE) had (HIS/HER) this fluoroscopy?
Record months or years for age

____ ____ MONTHS/YEARS

725. On how many occasions were other fluoroscopies taken of (HIS/HER) (UPPER BODY PART)?

____ ____ # OCCASIONS

Skip to QX 726

X-RAY TREATMENTS

These next questions are about x-ray treatments (SUBJECT) may have received. I am referring only to x-rays used to *treat* a condition, not to x-rays used to *diagnose* problems like broken bones or dental cavities. Please look at the last page of the *blue* Interview Booklet. Again, you will see a picture with a shaded portion I will refer to as the upper body.

Now let's turn to page 31 of the *blue* **Interview Booklet**, and think about any x-ray treatments (SUBJECT) may have had before age 15.

Review pages 31-32.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

When answering these questions, please remember that I am only interested in procedures done in this area of the body.

726. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Acne?**

YES

727. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for acne?
Record months or years for age

____ ____ MONTHS/YEARS

728. On how many different occasions did (SUBJECT) have x-ray treatments for acne?

____ ____ # OCCASIONS

729. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

NO

Skip to Ringworm, QX 730.

730. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Ringworm?**

YES

731. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for ringworm? ***Record months or years for age***

____ ____ MONTHS/YEARS

732. On how many different occasions did (SUBJECT) have x-ray treatments for ringworm?

____ ____ # OCCASIONS

733. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

NO

734. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Enlarged Tonsils?**

YES

735. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for enlarged tonsils? ***Record months or years for age***

____ ____ MONTHS/YEARS

736. On how many different occasions did (SUBJECT) have x-ray treatments for enlarged tonsils?

____ ____ # OCCASIONS

737. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

NO

Skip to Tuberculosis, QX 738

738. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Tuberculosis?**

YES / **NO**

739. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for tuberculosis?
Record months or years for age

____ ____ MONTHS/YEARS

740. On how many different occasions did (SUBJECT) have x-ray treatments for tuberculosis?

____ ____ # OCCASIONS

741. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

742. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Scalp Infection?**

YES / **NO**

743. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for scalp infection?
Record months or years for age

____ ____ MONTHS/YEARS

744. On how many different occasions did (SUBJECT) have x-ray treatments for scalp infection?

____ ____ # OCCASIONS

745. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

Skip to Enlarged Thymus, QX 746

746. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **Enlarged Thymus?**

YES — **NO**

747. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for enlarged thymus? ***Record months or years for age***

____ ____ MONTHS/YEARS

748. On how many different occasions did (SUBJECT) have x-ray treatments for enlarged thymus?

____ ____ # OCCASIONS

749. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

750. Before age 15, did (SUBJECT) ever have any radiation therapy or x-ray treatments to any part of (HIS/HER) upper body or head for **any other condition?**

YES — **NO**

751. For what other condition? ***Record Verbatim***

752. How old was (SUBJECT) when (HE/SHE) had the first x-ray treatment for (OTHER CONDITION)? ***Record months or years for age***

____ ____ MONTHS/YEARS

753. On how many different occasions did (SUBJECT) have x-ray treatments for (OTHER CONDITION)?

____ ____ # OCCASIONS

754. Was a lead apron usually placed over the neck area?

YES 1
NO 2
DK 9

Skip to Thyroid Scans, QX 755

THYROID SCANS

This next set of questions is about any thyroid scans (SUBJECT) may have had.

Let's turn to page 33 in the *blue* **Interview Booklet**, and think about any other diagnostic procedures (SUBJECT) may have had before age 15.

Review pages 33-34.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

755. Before age 15, did (SUBJECT) ever have a thyroid scan?

YES

NO → **Skip to Diagnostic Nuclear Medicine, QX 759**

756. What is the name and address of the physician who requested this thyroid scan?
Record Physician Name and Address

757. How old was (SUBJECT) when (HE/SHE) had (HIS/HER) first thyroid scan?
Record months or years for age

____ ____ MONTHS/YEARS

758. On how many occasions did (SUBJECT) have thyroid scans before age 15?

____ ____ # OCCASIONS

DIAGNOSTIC NUCLEAR MEDICINE

Now I will ask you about other nuclear medicine studies (SUBJECT) may have had as a child.

759. Before age 15, did (SUBJECT) ever take a radioactive substance by mouth or have one injected into a vein to diagnose a medical problem other than a thyroid problem?

YES / **NO**

760. How old was (SUBJECT) when (HE/SHE) had (HIS/HER) first procedure?
Record months or years for age

____ ____ MONTHS/YEARS

761. On how many occasions were these procedures performed?

____ ____ # OCCASIONS

Skip to Thyroid Problems, QX 762

THYROID PROBLEMS

Let's turn to page 35 in the *blue* **Interview Booklet**, and think about any thyroid problems (SUBJECT) may have had before age 15.

Review pages 35-36.

Please take your time to think about this topic. do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

I am now going to ask you some questions about any thyroid problems that (SUBJECT) may have had as a child.

762. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had **Graves' Disease or hyperthyroidism, that is, an over-active thyroid**?

YES — **NO**

NO → **Skip to QX 781, Hypothyroidism**

763. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

764. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age

____ ____ MONTHS/YEARS

765. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES — **NO**

NO → **Skip to QX. 769, Radiation Treatment for Graves' Disease or Hyperthyroidism**

YES

766. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

767. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years

____ ____ MONTHS/YEARS

768. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES — **NO**

YES → **Repeat QX. 766**

NO → **Skip to QX. 769**

769. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES

770. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

771. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

772. How many courses of radiation treatment were given?

____ ____ # COURSES

773. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

NO

Skip to QX. 774, Surgery for Graves' Disease or Hyperthyroidism

774. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES

775. When was the surgery performed for this condition?

____ ____ ____ ____
MONTH YEAR

776. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

NO

Skip to QX 777, Other Treatment for Graves' Disease or Hyperthyroidism

777. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?

YES **NO**

778. What was this treatment?
Record Verbatim

779. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years

____ ____ MONTHS/YEARS

Skip to 780, New Doctor

780. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?

YES **NO**

Repeat from QX 763.

Skip to 781, Hypothyroidism

781. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had **Hypothyroidism, that is, an under-active thyroid**?

YES / **NO**

NO → **Skip to QX 800, Malignant Thyroid Tumor or Lump**

YES

782. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

783. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age

____ ____ MONTHS/YEARS

784. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES / **NO**

NO → **Skip to QX 788, Radiation Treatment for Hypothyroidism**

YES

785. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

786. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years

____ ____ MONTHS/YEARS

787. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES / **NO**

YES → **Repeat QX 785**

NO → **Skip to QX 788**

788. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES / **NO**

789. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

790. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

791. How many courses of radiation treatment were given?

____ ____ # COURSES

792. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

Skip to QX 793, Surgery for Hypothyroidism

793. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES / **NO**

794. When was the surgery performed for this condition?

____ ____ ____ ____

MONTH YEAR

795. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

Skip to QX 796, Other Treatment for Hypothyroidism

796. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?

YES — **NO**

797. What was this treatment?
Record Verbatim

798. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years

____ ____ MONTHS/YEARS

Skip to 799, New Doctor

799. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?

YES — **NO**

Repeat from QX 782

Skip to 800, Malignant Thyroid Tumor or Lump

800. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had a **Malignant Thyroid Tumor or Lump**?

YES — **NO**

NO → **Skip to QX 819, Benign Thyroid Tumor or Lump**

YES

801. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

802. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age

____ ____ MONTHS/YEARS

803. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES — **NO**

NO → **Skip to QX 807, Radiation Treatment for Malignant Thyroid Tumor or Lump**

YES

804. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

805. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years

____ ____ MONTHS/YEARS

806. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES — **NO**

YES → **Repeat QX 804**

NO → **Skip to QX 807**

807. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES / **NO**

808. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

809. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

810. How many courses of radiation treatment were given?

____ ____ # COURSES

811. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

Skip to QX 812, Surgery for Malignant Thyroid Tumor or Lump

812. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES / **NO**

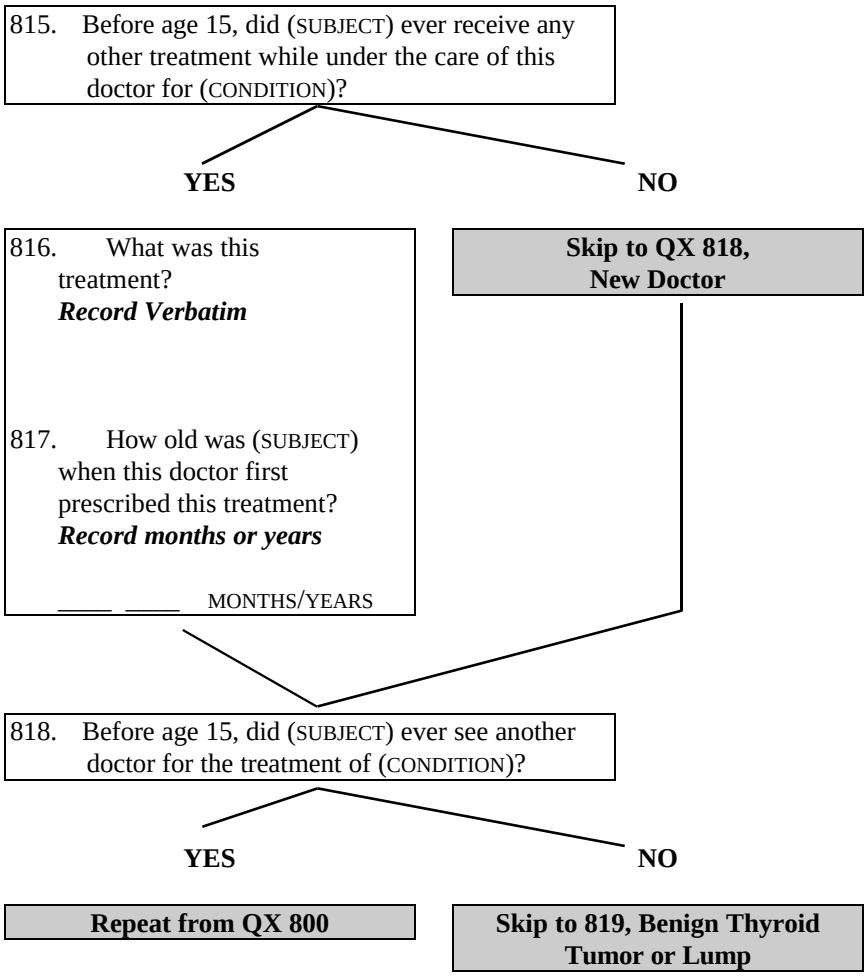
813. When was the surgery performed for this condition?

____ ____ ____ ____

MONTH YEAR

814. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

Skip to QX 815, Other Treatment for Malignant Thyroid Tumor or Lump


815. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?
YES
NO
816. What was this treatment?
Record Verbatim
817. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years
____ ____ MONTHS/YEARS
Skip to QX 818, New Doctor
818. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?
YES
NO
Repeat from QX 800
Skip to 819, Benign Thyroid Tumor or Lump

819. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had a **Benign Thyroid Tumor or Lump**?

YES — **NO**

NO → **Skip to QX 838, Goiter**

YES

820. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

821. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age

____ ____ MONTHS/YEARS

822. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES — **NO**

NO → **Skip to QX 826, Radiation Treatment for Benign Thyroid Tumor or Lump**

YES

823. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

824. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years

____ ____ MONTHS/YEARS

825. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES — **NO**

YES → **Repeat QX 823**

NO → **Skip to QX 826**

826. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES

827. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

828. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

829. How many courses of radiation treatment were given?

____ ____ # COURSES

830. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

NO

Skip to QX 831, Surgery for Benign Thyroid Tumor or Lump

831. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES

832. When was the surgery performed for this condition?

____ ____ ____ ____

MONTH YEAR

833. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

NO

Skip to QX 834, Other Treatment for Benign Thyroid Tumor or Lump

834. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?

YES — **NO**

835. What was this treatment?
Record Verbatim

836. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years

____ ____ MONTHS/YEARS

Skip to QX 837, New Doctor

837. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?

YES — **NO**

Repeat from QX 820

Skip to QX 838, Goiter

838. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had **Goiter**?

YES — **NO**

NO → **Skip to QX 857, Other Thyroid Problem**

YES

839. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

840. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age

____ ____ MONTHS/YEARS

841. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES — **NO**

NO → **Skip to QX 845, Radiation Treatment for Goiter**

YES

842. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

843. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years

____ ____ MONTHS/YEARS

844. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES — **NO**

YES → **Repeat QX 842**

NO → **Skip to QX 845**

845. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES

846. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

847. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

848. How many courses of radiation treatment were given?

____ ____ # COURSES

849. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

NO

Skip to QX 850, Surgery for Goiter

850. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES

851. When was the surgery performed for this condition?

____ ____ ____ ____
MONTH YEAR

852. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

NO

Skip to QX 853, Other Treatment for Goiter

853. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?

YES **NO**

854. What was this treatment?
Record Verbatim

855. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years

____ ____ MONTHS/YEARS

Skip to QX 856, New Doctor

856. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?

YES **NO**

Repeat from QX 839

Skip to QX 857, Other Thyroid Problem

857. Before age 15, did a doctor ever tell (SUBJECT) that (HE/SHE) had **any other thyroid problem**?

YES / **NO**

Skip to QX 877, Dental X-rays

858. What was the problem or condition?
Record Verbatim

859. What is the name and address of this doctor?
Probe for status of practice, new M.D., etc.
Record verbatim.

860. How old was (SUBJECT) when (HE/SHE) was (FIRST DIAGNOSED/FIRST SEEN) by this doctor for (CONDITION)?
Record months or years for age
____ ____ MONTHS/YEARS

861. Before age 15, was (SUBJECT) ever given any medication by this doctor for the treatment of this condition?

YES / **NO**

Skip to QX 865, Radiation Treatment for Other Condition

862. What was the (FIRST/NEXT) kind of medication this doctor prescribed for this condition?
Record verbatim

863. How old was (SUBJECT) when (THIS DOCTOR) first prescribed this medication?
Record months or years
____ ____ MONTHS/YEARS

864. Before age 15, did this doctor prescribe another kind of medication for this condition?

YES / **NO**

Repeat QX 862

Skip to QX 865

865. Before age 15, did (SUBJECT) ever receive any radiation treatment while under the care of this doctor for (CONDITION)?

YES | **NO**

866. What type of radiation treatment did this doctor prescribe for this condition? ***Probe for external, internal, combined. Record Verbatim***

867. How old was (SUBJECT) when (HE/SHE) first had radiation treatment while under the care of this doctor? ***Record months or years***

____ ____ MONTHS/YEARS

861. How many courses of radiation treatment were given?

____ ____ # COURSES

869. What is the name and address of the hospital or facility where the radiation treatment was given? ***Record name and address.***

Skip to QX 870, Surgery for Other Condition

870. Before age 15, did (SUBJECT) ever have surgery while under the care of this doctor for (CONDITION)?

YES | **NO**

871. When was the surgery performed for this condition?

____ ____ ____ ____
MONTH YEAR

872. What is the name and address of the hospital or facility where the surgery was performed? ***Record Hospital Name and Address***

Skip to QX 873, Other Treatment for Condition

873. Before age 15, did (SUBJECT) ever receive any other treatment while under the care of this doctor for (CONDITION)?

YES | **NO**

874. What was this treatment?
Record Verbatim

875. How old was (SUBJECT) when this doctor first prescribed this treatment?
Record months or years

____ ____ MONTHS/YEARS

Skip to 876, New Doctor

876. Before age 15, did (SUBJECT) ever see another doctor for the treatment of (CONDITION)?

YES | **NO**

Repeat from QX 858

Skip to 877, Dental X-rays

DENTAL X-RAYS

Let's turn to page 37 in the *blue* **Interview Booklet**, and think about any dental x-rays (SUBJECT) may have had before age 15.

Review pages 37-38.

Please take your time to think about this topic. Do you have any thoughts you would like to share, or any questions? ***(pause)*** Should we continue with the interview now?

877. Did (SUBJECT) ever go to the dentist before age 15?

YES — **NO** → **Skip to QX 882**

878. Before age 15, did (HE/SHE) ever have x-rays taken of (HIS/HER) teeth?

YES — **NO** → **Skip to QX 882**

879. How old was (SUBJECT) when (HE/SHE) first had a dental x-ray taken?

Record months or years for age

__ __ MONTH/YEAR

880. Up to age 15, on how many occasions did (SUBJECT) have dental x-rays taken?

__ __ # OCCASIONS

881. Was a lead apron usually placed over the neck area?

YES.....1
NO.....2
DK.....9

INTERVIEWER CHECK

882. The quality of R's response was:

High Quality	**1**	**Skip to next section**
Generally Reliable	**2**	**Skip to next section**
Questionable	**3**	
Unreliable	**4**	

883. What is the main reason for the unreliable or questionable quality of this section of the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

884. How often was explanation text repeated?

Very often	**1**
Often	**2**
Not often	**3**
Not applicable	**4**

SECTION IX. FAMILIARITY/BIAS
(QX 900-906)

We have now completed the formal interview, and I have just a few more questions to ask.

900. How helpful were the materials in preparing for the interview?

- Very helpful 01
- Generally helpful 02
- Somewhat helpful 03
- Not very helpful 04
- Not at all helpful 05
- Don't Know 09

901. Overall, how accurate do you think you were able to be in answering the questions in this interview? ***Read List***

- Very Accurate 01
- Generally Accurate 02
- Somewhat Accurate 03
- Not Very Accurate 04
- Not at all Accurate 05
- Don't Know 09

902. What, if anything, do you feel contributes to a person developing thyroid disease? ***Do NOT read list***. ***Record and code all that apply***.

- Radiation Exposure 01
- Medical X-Rays or Radiation Treatment 02
- Family History/Genetics 03
- Lack of Iodine in the Diet 04
- Too Much Iodine in the Diet 05
- Being Overweight 06
- Pregnancy 07
- Puberty/Menopause 08
- Other Illnesses 09
- Medications 10
- Other (***Record Verbatim***) 11
- Don't Know 99

903. Please tell me all the types of health problems, if any, you feel may be caused by radiation released from Hanford.
Do NOT read list. Record and code all that apply.

Thyroid Diseases

Underactive Thyroid 01
Overactive Thyroid 02
Graves' Disease 03
Thyroid Cancer 04
Goiter 05
Thyroid Nodules (not cancer) 06

Other Cancers

Leukemia/Lymphoma 07
Breast Cancer 08
Lung Cancer 09
Colon Cancer 10
Other Cancer (*Specify*: _____). 11
All Cancer 12

Fertility/Genetic Disorders

Miscarriage 13
Infertility 14
Birth Defects (*Specify*: _____). 15
Genetic Defects Passed on to Offspring 16

Other

Multiple Sclerosis (MS) 17
Immune System Disease 18
Allergies 19
Skin Diseases (other than cancer) 20
Mental Retardation 21
None 22
Other (***Record Verbatim***) 23
Don't Know 99

904. How knowledgeable do you think you are about radiation released from Hanford?
Read list

- Very Knowledgeable 1
- Generally Knowledgeable 2
- Somewhat Knowledgeable 3
- Not Very Knowledgeable 4
- Not at all Knowledgeable 5
- Don't Know 9

905. **Question Deleted**

906. Do you believe the health of anyone in your family has been affected by radiation from Hanford?

- Yes 1
- No 2
- Don't Know 9

SECTION X. CONCLUDING REMARKS
(QXS 1000-1003)

1000. Do you have any questions or comments you would like to add before we end the interview?

YES

1001. ***Record Verbatim***

NO

SKIP TO QX 1002

1002. Would you like to be placed on our mailing list so that you can receive regular updates of the study's progress?

YES.....1
NO.....2
ALREADY ON MAILING LIST 3

1003. Would you like a copy of the study results?

YES.....1
NO.....2

CLOSING COMMENTS:

Once the study is completed and the data analyzed, we will be publishing the composite results from all of the study participants. No data on individuals will be released. No participant names will be released. As required by law, all of the information you have given me will be kept strictly confidential.

Someone from my office may call you in the future to ask a few questions directly from this interview as a quality control check of my work. This is the end of the interview. I want to thank you very much for your cooperation.

TIME INTERVIEW ENDED: ____ ____ : ____ ____ A.M. / P.M.

SECTION XI: INTERVIEWER COMMENTS
(QXS 1100-1102)

1100. R's cooperation was:

VERY GOOD	**1**	
GOOD	**2**	
FAIR	**3**	
POOR	**4**	

1101. Overall quality of R's response was::

HIGH QUALITY	**1**	**End**
GENERALLY RELIABLE	**2**	**End**
QUESTIONABLE	**3**	
UNRELIABLE	**4**	

1102. What is the main reason for the unreliable or questionable quality the interview?

Unclear memory of events	**1**
Uncertain understanding of questions	**2**
Hurried responses	**3**
Other, specify	**4**
Don't Know	**9**

FRED HUTCHINSON CANCER RESEARCH CENTER/
CENTERS FOR DISEASE CONTROL

ID# __ __ __ __ __ __ __ __ __ __ __ __

CONSENT TO PARTICIPATE IN

THE HANFORD THYROID DISEASE STUDY

HANFORD THYROID DISEASE STUDY

Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-425
Seattle, Washington 98104

Phone: 1-800-638-4837 (206) 667-5733

PRINCIPAL INVESTIGATOR:
SCOTT DAVIS, Ph.D.

CO-INVESTIGATORS:
KENNETH KOPECKY, Ph.D.
TOM HAMILTON, M.D., Ph.D.
BRUCE AMUNDSON, M.D.

Investigators Statement

This is a study about thyroid disease in people who may have been exposed to radioactive iodine released from the Hanford Nuclear Site from 1944-1957. The primary purpose of this study is to find out if some people developed thyroid diseases because of this exposure. In addition, we will also determine if some people may have developed parathyroid disease since this gland lies adjacent to the thyroid gland. We believe the information gathered here will help determine whether living near Hanford from 1944-1957 has resulted in an increased risk of developing thyroid disease.

If you agree to participate, we will ask that you take part in an interview, and to have a thyroid ultrasound scan, a thyroid examination, and a blood sample collected. An explanation of the thyroid ultrasound scan and a request for consent to perform this procedure are in a separate consent form.

The interview will be with a member of the research staff, and will take about 45 minutes. We will ask questions about where you have lived and worked, your smoking habits, dental history, and other questions about your general health. A small number of participants will be recontacted at a later date and asked a few questions to verify that the interview was conducted and all questions were asked.

The thyroid examination will be done by two medical doctors who specialize in thyroid disease. They will feel (palpate) your thyroid gland while you swallow water. It usually takes about 10 to 20 minutes for an exam. The examination is not painful and there are no risks or side effects from it. The results will be explained to you at the clinic after the examination. There is no charge for this examination.

If something abnormal is found during the examination, the doctors will explain to you what they think is wrong, and what they feel you should do next. They may recommend that you have additional tests. The types of additional tests they may want to perform include a fine needle aspiration, which they would want to do while you are at the clinic; or a thyroid nuclear scan, which would be done at a local clinic or hospital on another day. In the event that you do receive medical care for a thyroid or parathyroid abnormality as a result of participating in this study, we will request that you provide access to the medical records so that we may learn about your treatment. If such circumstances arise, it will be important for

us to stay in contact with you for a few months after your evaluation with us so that we receive all the records available as a result of the care you receive.

We will inform you of the results from examinations and tests in writing. In addition, the results will be sent to your personal doctor unless you do not want this done. If you do not have your own doctor, we will provide you with a list of physician referral resources in your area.

While you are at the clinic you will be asked to give a small blood sample to check your thyroid and parathyroid function. Three tubes of blood (a total of 30ml or about 2 tablespoons) will be withdrawn through a single needle stick from a vein in your arm by a doctor, a nurse, or a person certified to draw blood. This could cause some minor discomfort and/or leave a temporary bruise. There is no charge for the blood test. If you are experiencing a medical emergency because of the blood draw, dial 911 or your local operator for emergency assistance.

You may be contacted again during the next six weeks and asked to give a second blood sample. This would depend on what the first blood test showed about your thyroid or parathyroid function. This second blood test could be done in your community at your convenience. In the rare case of physical injury from the blood drawing procedure, financial compensation is not available. There is no charge for the additional blood test. If you are found to have an elevated calcium level on the second test, you will be asked to see your physician for additional diagnostic testing and treatment at your own expense. The study nurse or physicians will assist you in this process.

Only investigators from the Centers for Disease Control and Fred Hutchinson Cancer Research Center, members of the staff directly involved with this study, and staff of the quality control firm chosen to audit the data collection, will have access to the information we gather. The information you give will be combined with that given by other participants. It will be used in a statistical format when published in reports or medical journals. Therefore, none of the information supplied by a single individual will be recognizable. All information will be kept strictly confidential as required by public law PHS Act Section 308(d)(42 USC 242m(d)).

Your participation in this study is completely voluntary. Some questions in the interview are of a personal nature; you may refuse to answer any particular question or end the interview at any time. You are free to decide not to participate, and may withdraw from the study at any time without penalty.

The authorities for collecting the information in this study are Sections 301 and 306 of the Public Health Service Act. Furnishing the information, including your Social Security number (SSN), is voluntary. The SSN will be an additional item of identifying information that will assist in locating your medical records.

You will also be asked to provide information regarding your religious preference. Rates of disease have been shown in epidemiological studies to differ in members of certain religious groups which observe dietary and lifestyle restrictions. Therefore, the information on religion may be helpful in determining such differences. As with any of the questions asked, you may refuse to answer any or all of the questions, and there will be no adverse effect on you.

Through your participation in this study, you will receive a complete diagnostic work-up for thyroid disease, including an examination and laboratory testing. This includes: physical exam of thyroid gland, and blood tests for free thyroxine index (which includes total levothyroxine (T4) and resin T3 uptake), thyroid stimulating hormone (TSH), antibody to thyroid peroxidase enzyme, and serum calcium. In addition, if further diagnostic testing is recommended to determine a thyroid diagnosis, this will also be done at no cost to you. This could include any of the following: Technetium-99m scan *or* Iodine-123 scan and fine needle aspiration of the thyroid.

You will be reimbursed for travel expenses associated with your participation in this study. The knowledge gained through your participation in this study will further our understanding of the relationship between radiation and thyroid disease.

If you have questions about your rights as a research participant, please contact Karen Hansen in the Institutional Review Office of the Fred Hutchinson Cancer Research Center at (206) 667-4867. Collect calls are accepted.

If you have any questions while at the clinic, or need assistance with a medical referral, please speak with the Field Operations Coordinator. After you leave the clinic, please call 1-800-638-4837 if you have further questions.

_____ _____

SIGNATURE OF HTDS STAFF MEMBER DATE

Participant's Statement

The study has been explained to me. I have had the opportunity to ask questions. I understand that future questions I may have about the research will be answered by one of the investigators listed above. Any questions I have about my rights as a research participant will be answered by Ms. Karen Hansen. Any questions I have while at the clinic will be answered by the Field Operations Coordinator. After leaving the clinic, I may call 1-800-638-4837 with further questions. I am aware that in the event of physical injury as a result of my participation in this study, financial compensation is not available. I may refuse to answer any questions or decide not to complete the interview if I wish. I may decide not to have the thyroid exam or have my blood drawn if I wish. I voluntarily consent to participate in this study and have received a copy of this consent form.

_____ _____

SIGNATURE OF PARTICIPANT DATE

Request that Results NOT be Provided to Personal Physician

I understand that it is the policy of the Hanford Thyroid Disease Study to provide my personal doctor with copies of all examination and test results from my participation in this study and to contact my personal doctor by telephone if any results are not normal. I understand that the intention of this policy is to ensure that my doctor has all information necessary to provide for my continuing medical care.

My signature below indicates that **I have refused my permission for copies of any examination or test results to be provided to my personal doctor.**

_____ _____

SIGNATURE OF PARTICIPANT DATE

_____ _____

SIGNATURE OF CLINIC OPERATIONS COORDINATOR DATE

1 copy to participant
1 copy to study files

HTDS THYROID ULTRASOUND FORM

SUBJECT I.D. #: _ _ _ _ _ _ _ _ _ _

ULTRASOUND TECH: 01 02 03 04 05

DATE OF ULTRASOUND: __ __ __ __ __ __

TAPE COUNT: ___ - ___

RADIOLOGIST COMPLETES

RADIOLOGIST: 01 02 03 04 05 06

DATE ULTRASOUND REVIEWED: __ __/__ __/__ __

1. ULTRASOUND PERFORMED

1 .....YES
2 .....NO

IF YES,

Y N THYROID VISIBLE
Y N EXAM ADEQUATE

IF NO, REASON:

1 .....REFUSED
2 .....OTHER (SPECIFY)

2. THYROID SIZE

	RIGHT	LEFT
LENGTH (CM)	__.__	__.__
WIDTH (CM)	__.__	__.__
HEIGHT (CM)	__.__	__.__
MASS (GM) (L X W X H X .55)	__.__	__.__
AP THICKNESS OF ISTHMUS (CM)		___.___

COMMENT:

3. NODULARITY

1 .....YES
2 .....NO
3 .....UNCERTAIN

COMMENT:

4. OTHER ABNORMALITIES

0	< 10	≥ 10	
	Y	N	Diffuse Abnormalities
	Y	N	Other, specify

Comments:

RADIOLOGIST COMMENT:

nodularity ≥5mm..... agree .... disagree

nodularity <5mm..... agree .... disagree

diffuse abnormality..... agree .... disagree

5. GENERAL COMMENTS

1 .....YES
2 .....NO

6. EXPOSURE STATUS

AWARENESS OF POSSIBLE EXPOSURE STATUS:
1 .....NONE
2 .....POSSIBLE
3 .....DEFINITE

IF POSSIBLE/DEFINITE, APPARENT EXPOSURE:
1 ..... NONE/VERY LOW
2 ..... INTERMEDIATE
3 ..... HIGH
4 ..... UNKNOWN

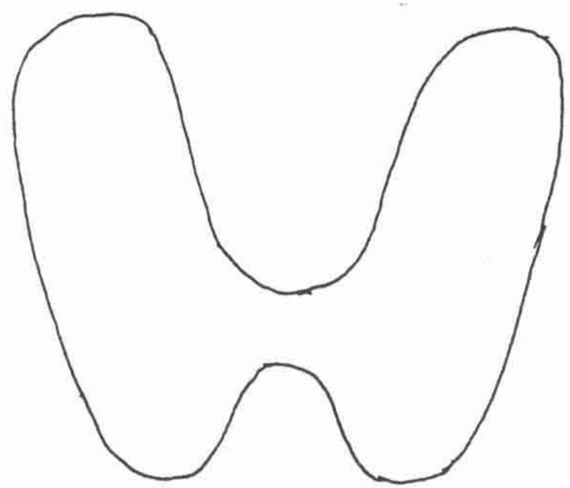
7. CHARACTERIZATION OF NODULES ≥ 5 mm

NODULE I.D.	LOCATION	SIZE (CM)	PALPABLE
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U
____	____________	_._X_._X_._	Y N U

RADIOLOGIST COMMENT ONLY

DETECTION STATUS	TYPE	IF SOLID, ECHOGENICITY	IF SOLID, HALO	CALCIF-ICATION
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N
C D N NS	S C M	Hr Ho I	C P N	Y N

Identify Nodules as 1, 2, 3, etc.



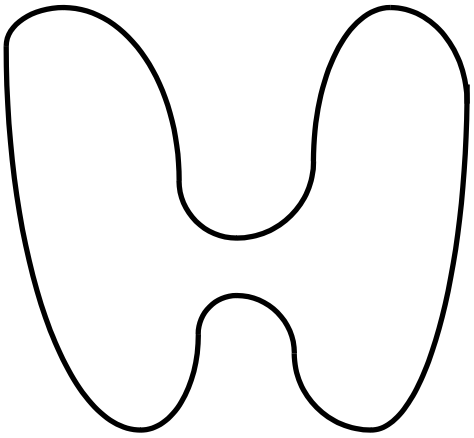
● SOLID
○ CYSTIC
⊗ MIXED

DETECTION STATUS	TYPE	ECHOGENICITY	HALO
C = CONFIRMED	S = SOLID	HR = HYPERECHOIC	C = COMPLETE
D = DISAGREE	C = CYSTIC	HO = HYPOECHOIC	P = PARTIAL
N = NEW	M = MIXED	I = ISOECHOIC	N = NO
NS = NOT SEEN			

RADIOLOGIST COMMENTS

SUBJECT I.D. #: _ _ _ _ _ _ _ _ _ _ _   DATE KEY ENTERED: _ _/_ _/_ _   KEY ENTRY I.D. #: _ _   03/29/94

Appendix 13

IDENTIFY DISCRETE NODULES AS #1, #2 AND #3, CORRESPONDING to REVERSE SIDE of this FORM	**HTDS THYROID EXAMINATION FORM**
	SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __ EXAMINER: 01 02 03 04 05 06 DATE OF EXAM: ___ ___ ___ ___ ___ ___ MONTH DAY YEAR

COMPLETE EACH ITEM; ADD COMMENTS AS NECESSARY

1. EVIDENCE OF THYROID SURGICAL SCAR PRESENT

1.....YES 2.....NO 3.....UNCERTAIN	*COMMENT:*

2. LYMPH NODE EXAM

1.....NORMAL 2.....ABNORMAL 3.....UNCERTAIN	*COMMENT:*

3. THYROID EXAM

1.....NORMAL 2.....ABNORMAL 3.....BORDERLINE 4.....THYROID NOT PALPABLE 5.....EXAM NOT ADEQUATE ***If 1, 4 or 5 Above, Skip to Item 7***	*COMMENT:*

4. THYROID ENLARGEMENT

1.....YES 2.....NO 3.....UNCERTAIN ____ . ____ ESTIMATE OF X-FOLD ENLARGEMENT	*COMMENT:*

5. NODULARITY

A. NUMBER OF DISCRETE NODULES: ____ ____ B. MULTINODULAR GOITER: 1.....YES 2.....NO 3.....UNCERTAIN *If no Discrete Nodules Present, Skip to Item 7*	*COMMENT:*

6. CHARACTERIZATION OF DISCRETE NODULES

NODULE #	LOCATION	SIZE	CONSISTENCY	CONTOUR	SHAPE
_____	R L I	__ . __ x __ . __	S F H O	S G O	R I
_____	R L I	__ . __ x __ . __	S F H O	S G O	R I
_____	R L I	__ . __ x __ . __	S F H O	S G O	R I

COMMENTS:

7. CLINICAL EXAM IMPRESSION

1 .....NORMAL
2 .....SIMPLE GOITER
3 .....SOLITARY NODULE
4 .....MULTINODULAR GOITER
6 .....NONPALPABLE THYROID
7 .....EVIDENCE OF THYROID SURGERY
8 .....UNCERTAIN
9 .....OTHER (*Specify*: _____)

COMMENT:

8. GENERAL COMMENTS

1 .....YES
2 .....NO

9. EXPOSURE STATUS

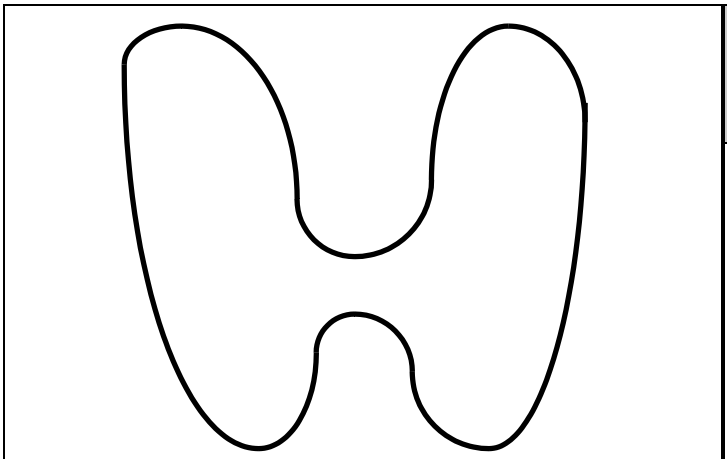
AWARENESS OF POSSIBLE EXPOSURE STATUS:

1 .....NONE
2 .....POSSIBLE
3 .....DEFINITE

IF POSSIBLE/DEFINITE, APPARENT EXPOSURE:

1..... NONE/VERY LOW
2..... INTERMEDIATE
3..... HIGH
4..... UNKNOWN

SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __ __ DATE KEY ENTERED: __ __ / __ __ / __ __ KEY ENTRY ID #: ___ ___ *version 03/07/94*



HANFORD THYROID DISEASE STUDY

CONSENSUS EXAMINATION FORM

SUBJECT ID # __ __ __ __ __ __ __ __ __ __ __ __

EXAMINERS 01 02 03 04 05 06
CIRCLE ALL THAT APPLY

DATE OF EXAM ___ ___ ___ ___ ___ ___
MONTH DAY YEAR

COMPLETE EACH ITEM; ADD COMMENTS AS NECESSARY

1. CONSENSUS EXAM PERFORMED

1 .....YES
2 .....NO
If NO, skip to 8

COMMENT:

2. EVIDENCE OF THYROID SURGICAL SCAR PRESENT

1 .....YES
2 .....NO
3 .....UNCERTAIN

COMMENT:

3. THYROID EXAM

1 .....NORMAL
2 .....ABNORMAL
3 .....BORDERLINE
4 .....THYROID NOT PALPABLE
5 .....EXAM NOT ADEQUATE
If 1, 4 or 5, skip item 7

COMMENT:

4. THYROID ENLARGEMENT

1 .....YES
2 .....NO
3 .....UNCERTAIN
_____ . _____ MEAN X-FOLD ENLARGEMENT

COMMENT:

5. NODULARITY

A. NUMBER OF DISCRETE NODULES: ____ ____
B. MULTINODULAR GOITER:
1.....YES
2.....NO
3.....UNCERTAIN

COMMENT:

6. MEAN SIZE OF NODULE

NODULE #1 ____ . ____ CM

NODULE #2 ____ . ____ CM

NODULE #3 ____ . ____ CM

COMMENT:

7. CLINICAL EXAM IMPRESSION

1 .....NORMAL
2 .....SIMPLE GOITER
3 .....SOLITARY NODULE
4 .....MULTINODULAR GOITER
6 .....NONPALPABLE THYROID
7 .....EVIDENCE OF THYROID SURGERY
8 .....UNCERTAIN
9 .....OTHER (SPECIFY)

COMMENT:

8. GENERAL COMMENTS

1 .....YES
2 .....NO

SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __ __ **DATE KEY ENTERED: __ __ / __ __ / __ __** **KEY ENTRY ID#: ___ ___** ***03/07/94***

HANFORD THYROID DISEASE STUDY

THYROID ULTRASOUND SCAN FACT SHEET

The Results of Your Ultrasound Scan

As the Hanford Thyroid Disease Study (HTDS) physicians discussed with you at your clinic visit, your thyroid examination was normal, but your thyroid ultrasound scan indicated that you have one or more small abnormalities. This result by itself does not necessarily mean you have thyroid disease. All of your test results from the clinic will need to be reviewed before we can provide you with our final evaluation.

What You Can Expect

Medical review of all of your clinic results, including your blood test results and thyroid ultrasound scan, occurs after your clinic visit. Radiologists working with the HTDS physicians will interpret your thyroid ultrasound scan. After the medical review is completed, you will be sent a letter explaining all of your results with recommendations by the HTDS physician. Copies of your test results will be included with your final evaluation results letter.

If you have any concerns or questions, please call our toll-free number, 1-800-XXX-XXXX.

I.D. LABEL

IN-PERSON QUESTIONNAIRE - STANDARD VERSION

HANFORD THYROID DISEASE STUDY

PHASE	INITIALS	DATE
EDITED	_____	_____
CODED	_____	_____
KEYED	_____	_____
VERIFIED	_____	_____

SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __ __
TIME BEGUN: __ __ : __ __ A.M. / P.M.
QUESTIONNAIRE VERSION #: 12/11/95 06
INTERVIEWER ID: _____
BIRTHDATE (mm/dd/yy): __ __ / __ __ / __ __
CLINIC LOCATION: _____
CLINIC CODE: ___ ___
DATE OF INTERVIEW ___ ___ / ___ ___ / ___ ___
INTERVIEW OUTCOME: ___
1 = COMPLETE
2 = PARTIAL COMPLETE

FORM APPROVED: OMB NUMBER: 0920-0296
EXP. DATE: May 31, 1998

My name is (INTERVIEWER'S NAME). I'm one of the interviewers for the Hanford Thyroid Disease Study. I'll be asking you some questions about your residential, medical, and occupational history, along with some other questions. In this interview we're only concerned with the time period from age 15 to the current time because we've already received information about your early childhood from the person you selected for the telephone interview. Before we begin there are a few things I need to mention:

- All of the information you provide will be kept strictly confidential as required by public law PHS Act Section 308(d)(42 USC 242m(d)).
- Try to be as accurate as possible when answering the questions. Don't feel rushed, and do not hesitate to ask me to repeat a question.
- If you choose not to answer a question, simply tell me and we will move on to the next question.
- You may end the interview at any time.

Do you have any questions before we begin? ***(Answer questions)*** My job as the interviewer is to read the questions exactly as they are written. For this reason, please wait until after I've read the complete question before giving me your answer. ***(Begin the interview.)***

SECTION I: RESIDENCE HISTORY

(QXS 100-115)

I'd like to begin by asking you questions about some places you may have lived between January 1, 1958 and the present. If you have the interview preparation worksheet, please refer to it for this section.

(For each YES, ask questions 111-115)

100. Since 1958, have you lived in Nevada?
101. Since 1958, have you lived in Utah?
102. Since 1958, have you lived in Arizona?
103. Since 1958, have you lived in New Mexico?
104. Since 1958, have you lived in Colorado?
105. Since 1958, have you lived in Idaho?
106. Since 1958, have you lived in Ohio?
107. Since 1958, have you lived in South Carolina?
108. Since 1958, have you lived in Tennessee?
109. Did you live in the Marshall Islands at anytime in 1958 or 1959?
110. Did you live in Pennsylvania at anytime in 1979?

Interviewer:
111. Enter 2-digit state abbreviation.

112. What county did you live in?
If county not known, ask: **What town did you live in?**
113. In what month and year did you (first/next) move to (County/City) in (State)?
114. In what month and year did you (first/next) move out of (County) in (State)?
115. Did you ever live in (State) at any other time?

SECTION II: OCCUPATIONAL HISTORY
(QXS 200-212)

Now I'm going to ask you some questions about your employment history.

200. Have you ever worked in any of the following industries or occupations?
(For each YES, ask questions 201-210)
a. Geology?
b. Metallurgy?
c. Metal Processing?
d. Ore Refining?
e. Mining?
f. In the nuclear industry, as a civilian?
g. On the premises of a nuclear facility?
h. In health care, with exposure to radioactive materials or x-rays?
i. As a scientist, Researcher, or Student with exposure to radioactive materials or x-rays?
j. In the military, working around nuclear testing, nuclear submarines, or other radiation exposure?
k. Have you worked in any other industry or occupation where you may have been exposed to radioactive materials or x-rays?
201. What was the name of the company or organization you worked for?

Interviewer: Skip to QX 203 if same field
202. Have you already told me about this particular job?
203. In which city and state was your job?

204. What did this company or organization make or do?
205. What was your job title there?
206. What were your activities and duties as (JOB TITLE)?
207. When did you start there as a (JOB TITLE)?
208. When did you last work there as a (JOB TITLE)?
209. Was that full-time or part-time employment?
210. Have you ever worked in any other jobs in (SAME FIELD)?

211. What have been your primary occupations?
212. Other than through medical tests or procedures, have you **EVER** been exposed to any radiation that you know of?

SECTION III - SMOKING HISTORY
(QXS 300-321)

I'm going to ask you about smoking and tobacco use. The first series of questions is about cigarette use, and is divided into two parts. The first will ask about **NON-FILTER** cigarettes only, and the second will ask about **FILTER** cigarettes.

300. Have you ever smoked a total of 100 or more **NON-FILTER** cigarettes in your lifetime?
301. At what age did you (FIRST/NEXT) start smoking **non-filter** cigarettes?
302. Did you ever stop smoking **non-filter** cigarettes for six consecutive months or longer?
303a. How old were you when you (FIRST/NEXT) stopped smoking **non-filter** cigarettes?
304a. On the average, how many **non-filter** cigarettes did you smoke per day between age (QX 301) and age (QX 303a)?
305a. Did you ever start smoking **non-filter** cigarettes again?
303b. What is your current age?
304b. On the average, how many **non-filter** cigarettes have you smoked per day since age (QX 301)?
306. Have you ever smoked a total of 100 or more **FILTER** cigarettes in your lifetime?
307. At what age did you (FIRST/NEXT) start smoking **filter** cigarettes?
308. Did you ever stop smoking **filter** cigarettes for six consecutive months or longer?
309a. How old were you when you (FIRST/NEXT) stopped smoking **filter** cigarettes?
310a. On the average, how many **filter** cigarettes did you smoke per day between age (QX 307) and age (QX 309a)?
311a. Did you ever start smoking **filter** cigarettes again?
309b. What is your current age?
310b. On the average, how many **filter** cigarettes have you smoked per day since age (QX 307)?

The next questions are about smoking cigars and tobacco pipes.

312. Have you ever smoked **CIGARS** on a regular basis for six months or longer?
313. How old were you when you first started smoking cigars?
314. How old were you when you last smoked cigars?
315. From age (QX 313) to age (QX 314), how many total years did you smoke cigars?
316. How many would you usually smoke in a week?
317. Have you ever smoked tobacco in a **PIPE** on a regular basis for six months or longer?
318. How old were you when you first started smoking a pipe?
319. How old were you when you last smoked a pipe?
320. From age (QX 318) to age (QX 319), how many total years did you smoke a pipe?
321. How many bowls would you usually smoke in a week?

SECTION IV - DIAGNOSTIC MEDICAL PROCEDURES

(QXS 400-459)

The next set of questions is about **DIAGNOSTIC** medical procedures you may have had. I'll be asking you specific questions about different types of medical tests. If you don't understand a question, please let me know and I'll explain the procedure I'm asking about.

DIAGNOSTIC X-RAYS
(QXS 400-443)

First I'll be asking about radiologic procedures taken to diagnose a problem or condition of the upper body. I'm now referring to X-rays and CAT scans taken to diagnose broken bones or other conditions, not including routine dental X-rays. I'm only interested in diagnostic procedures you've had to the shaded portion of the body shown in the picture. ***Show Card 1***.

400. Since you turned 15 years of age, have you ever had a **CAT** scan of your upper body?
(If NO, skip to question 406)
401. Why was a CAT scan performed?
402. What area was scanned?
403. How many CAT scans were performed?
404. How old were you when you (first) had a CAT scan for (REASON)?
405. Did you ever have a CAT scan of your upper body for any other reason?

406. Since age 15, have you ever had any diagnostic x-rays taken of your **HEAD**? This would include head x-rays taken for orthodontic work and oral surgery, but would **NOT** include routine dental x-rays.
(If NO, skip to question 412)
407. Why was an x-ray taken?
408. On how many occasions were x-rays taken of your HEAD for (REASON)?
409. How old were you when you (first) had an x-ray taken of your HEAD for (REASON)?
410. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
411. Was an x-ray of your HEAD ever taken for any other reason?

412. Since age 15 have you ever had any diagnostic x-rays taken of your **NECK**?
(If NO, skip to question 417)
413. Why was an x-ray taken?
414. On how many occasions were x-rays taken of your NECK for (REASON)?
415. How old were you when you (first) had a NECK x-ray taken for (REASON)?
416. Was an x-ray of your NECK ever taken for any other reason?

417. Since age 15 have you ever had any diagnostic x-rays taken of your **CHEST or UPPER BACK** (including mammograms)? ***Show Card #1***
(If NO, skip to question 423)
418. Why was an x-ray taken?
419. (Since age 15) on how many occasions were x-rays taken of your CHEST or UPPER BACK for (REASON)?
420. (Since age 15) how old were you when you (first) had an x-ray taken for (REASON)?
421. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
422. (Since age 15) was an x-ray of your CHEST OR UPPER BACK (including mammograms) ever taken for any other reason?

423. Since age 15 have you ever had any diagnostic x-rays taken of your **STOMACH OR MID-BACK**?
(If NO, skip to question 429)
424. Why was an x-ray taken?

425. On how many occasions were x-rays taken of your STOMACH OR MID-BACK for (REASON)?
426. How old were you when you (first) had an x-ray taken for (REASON)?
427. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
428. Was an x-ray of your STOMACH OR MID-BACK ever taken for any other reason?

FLUOROSCOPIES
(QXS 429-449)

Fluoroscopy is a type of x-ray in which certain parts of the body are observed on a fluorescent screen, like a TV set. The doctor can view various parts of the body by watching the screen. A dye is sometimes used, and may be swallowed or injected into a vein. Fluoroscopy is used in a number of diagnostic procedures. I will ask you if you have had some procedures performed on the UPPER part of the body as shown in the picture ***(Show Card #1)***. I will also ask about barium enemas.

429. Since you turned 15 years of age, have you ever had a **BARIUM ENEMA**?
(If NO, skip to question 434)
430. Why did you have a Barium Enema?
431. How many Barium Enemas did you have for (REASON)?
432. How old were you when you (first) had a Barium Enema for (REASON)?
433. Was a Barium Enema ever done for any other reason?

434. Since age 15 have you ever had an **UPPER GI**?
(If NO, skip to question 429)
435. Why did you have an Upper GI?
436. How many Upper GIs did you have for (REASON)?
437. How old were you when you (first) had an Upper GI for (REASON)?
438. Was an Upper GI ever done for any other reason?

439. Since age 15 have you ever had an **INTRAVENOUS PYELOGRAM** or **IVP**?
(If NO, skip to question 444)
440. Why did you have an IVP?
441. How many IVPs did you have for (REASON)?
442. How old were you when you (first) had an IVP for (REASON)?
443. Was an IVP ever done for any other reason?

444. Since you turned 15 years of age, did you ever have any other fluoroscopies of your upper body?
(If NO, skip to question 450)
445. What part of the upper body?
446. Why did you have a fluoroscopy?
447. How many fluoroscopies did you have for (REASON)?
448. How old were you when you (first) had a fluoroscopy for (REASON)?
449. Was a fluoroscopy ever taken for any other reason?

THYROID SCANS AND OTHER NUCLEAR MEDICINE PROCEDURES
(QXS 450-458)

The next few questions are about diagnostic nuclear medicine procedures. These are sometimes called "scans". During these procedures, a radioactive substance is given by mouth or injected into a vein to make an area of the body show up on an x-ray in order to diagnose a medical problem.

450. Since you turned 15 years of age, have you ever had a **thyroid nuclear scan**?
(If NO, skip to question 455)
451. In what month and year did you have this thyroid nuclear scan?
452. What is the name of the physician who requested this thyroid nuclear scan?
453. May we have your consent to obtain pertinent medical records from your physician?
454. Did you have any other thyroid nuclear scans?

455. Since age 15, have you had any other NUCLEAR SCANS? (that is, a procedure in which a radioactive substance is given by mouth or injected into a vein to diagnose a medical problem?)
(If NO, skip to question 500)
456. What type of procedure was done?
457. Why was this procedure done?
458. In what month and year did you have this procedure?
459. Have you had any other nuclear scans?

SECTION V: THYROID PROBLEMS
(QXS 500-557)

The next set of questions is about thyroid disease. If you don't understand a question, please let me know and I'll describe the condition I'm asking about.

500. Has a **DOCTOR** ever told you that you had **GRAVES' DISEASE** or hyperthyroidism, that is, an **OVER**-active thyroid?
(If NO, skip to question 508)
501. At what age were you diagnosed with Graves' disease or over-active thyroid?
502. What is the full name of the physician who diagnosed this condition?
503. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for Graves' Disease or over-active thyroid.

504. (SINCE YOU TURNED 15 YEARS OF AGE) have you taken THYROID MEDICATION for Graves' Disease or an over-active thyroid?
(If NO, skip to question 505)
504.A. What kind of medication did you take for this condition?
504.B. How old were you when you **FIRST** took (MEDICATION) for over-active thyroid?
504.C. How old were you when you **LAST** took (MEDICATION) for this condition?
504.D. What are the names of all of the doctors who have prescribed (MEDICATION) for this condition?
504.E. May we have your consent to obtain pertinent medical records from your doctor?
504.F. (SINCE AGE 15) have you taken **ANY OTHER** thyroid medication for Graves' disease or an over-active thyroid?

505. (SINCE AGE 15), have you had THYROID SURGERY for Graves' Disease or over-active thyroid?
(If NO, skip to question 506)
505.A. How old were you when you had thyroid surgery for this condition?
505.B. What is the name of the hospital where you had this thyroid surgery?

505.C. May we have your consent to obtain pertinent medical records from the hospital?

506. (SINCE AGE 15), have you had THYROID RADIATION TREATMENT for Graves' Disease or over-active thyroid?
(If NO, skip to question 507)

506.A. How old were you when you **FIRST** had thyroid radiation treatment for this condition?
506.B. How old were you when you **LAST** had thyroid radiation treatment for this condition?
506.C. What are the names of the clinics or hospitals where you had this radiation treatment?
506.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

507. (SINCE AGE 15), have you had ANY OTHER TYPE of thyroid treatment for Graves' Disease or over-active thyroid?
(If NO, skip to question 508)

507.A. What type of treatment did you have for this condition?
507.B. How old were you when you **FIRST** had (TREATMENT) for this condition?
507.C. How old were you when you **LAST** had (TREATMENT) for this condition?
507.D. What is the name of the doctor who ordered (TREATMENT)?
507.E. May we have your consent to obtain pertinent medical records from your doctor?

508. Has a **DOCTOR** ever told you that you were hypothyroid, that is, had an **UNDER**-active thyroid?
(If NO, skip to question 516)
509. At what age were you diagnosed with an under-active thyroid?
510. What is the full name of the physician who diagnosed this condition?
511. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for an under-active thyroid.

512. (SINCE YOU TURNED 15 YEARS OF AGE), have you taken THYROID MEDICATION for an under active thyroid?
(If NO, skip to question 513)

512.A. What kind of medication did you take for under-active thyroid?
512.B. How old were you when you **FIRST** took (MEDICATION) for under-active thyroid?
512.C. How old were you when you **LAST** took (MEDICATION) for under-active thyroid?
512.D. What are the names of all of the doctors who have prescribed (MEDICATION) for under-active thyroid?
512.E. May we have your consent to obtain pertinent medical records from your doctor?
512.F. (SINCE AGE 15) have you taken **ANY OTHER** thyroid medication for an under-active thyroid?

513. (SINCE AGE 15), have you had THYROID SURGERY for under-active thyroid?
(If NO, skip to question 514)

513.A. How old were you when you had thyroid surgery for under-active thyroid?
513.B. What is the name of the hospital where you had thyroid surgery for under-active thyroid?
513.C. May we have your consent to obtain pertinent medical records from this hospital?

514. (SINCE AGE 15), have you had THYROID RADIATION TREATMENT for under-active thyroid?
(If NO, skip to question 515)

514.A. How old were you when you **FIRST** had thyroid radiation treatment for under-active thyroid?
514.B. How old were you when you **LAST** had thyroid radiation treatment for under-active thyroid?
514.C. What are the names of the clinics or hospital where you had radiation treatment for under active thyroid?
514.E. May we have your consent to obtain pertinent medical records from the clinic or hospital?

515. (SINCE AGE 15), have you had ANY OTHER TYPE of thyroid treatment for under-active thyroid?

(If NO, skip to question 516)

515.A. What type of treatment did you have for under-active thyroid?
515.B. How old were you when you **FIRST** had (TREATMENT) for under-active thyroid?
515.C. How old were you when you **LAST** had (TREATMENT) for under-active thyroid?
515.D. What is the name of the doctor who ordered (TREATMENT) for under-active thyroid?
515.E. May we have your consent to obtain pertinent medical records from your doctor?

516. Has a **DOCTOR** ever told you that you had a **THYROID NODULE** or **TUMOR**?
(If NO, skip to question 525)
517. Was this thyroid nodule or tumor benign or malignant?
518. At what age were you diagnosed with a thyroid (CONDITION)?
519. What are the full names of the physicians who diagnosed this condition?
520. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for a thyroid (CONDITION).

521. (SINCE YOU TURNED AGE 15) have you taken thyroid MEDICATION for a thyroid (CONDITION)?
(If NO, skip to question 522)

521.A. What kind of medication did you take for a thyroid (CONDITION)?
521.B. How old were you when you **FIRST** took (MEDICATION) for a thyroid (CONDITION)?
521.C. How old were you when you **LAST** took (MEDICATION) for a thyroid (CONDITION)?
521.D. What are the names of all of the doctors who have prescribed (MEDICATION) for a thyroid (CONDITION)?
521.E. May we have your consent to obtain pertinent medical records from your doctor?
521.F. (SINCE AGE 15) have you taken any other thyroid medication for a thyroid (CONDITION)?

522. (SINCE AGE 15), have you had thyroid SURGERY for a thyroid (CONDITION)?
(If NO, skip to question 523)

522.A. How old were you when you had surgery for thyroid (CONDITION)?
522.B. What is the name of the hospital where you had thyroid surgery for thyroid (CONDITION)?
522.C. May we have your consent to obtain pertinent medical records from the hospital?

523. (SINCE AGE 15), have you had thyroid RADIATION TREATMENT for thyroid (CONDITION)?
(If NO, skip to question 524)

523.A. How old were you when you **FIRST** had thyroid radiation treatment for thyroid (CONDITION)?
523.B. How old were you when you **LAST** had thyroid radiation treatment for thyroid (CONDITION)?
523.C. What are the names of the clinics or hospital where you had radiation treatment for thyroid (CONDITION)?
523.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

524. (SINCE AGE 15), have you had ANY OTHER TYPE of thyroid treatment for thyroid (CONDITION)?
(If NO, skip to question 525)

524.A. What type of treatment did you have for thyroid (CONDITION)?
524.B. How old were you when you **FIRST** had (TREATMENT) for thyroid (CONDITION)?
524.C. How old were you when you **LAST** had (TREATMENT) for thyroid (CONDITION)?
524.D. What is the name of the doctor who ordered (TREATMENT) for thyroid (CONDITION)?
524.E. May we have your consent to obtain pertinent medical records from your doctor?

525. Has a **DOCTOR** ever told you that you had a **GOITER?**
(If NO, skip to question 553)
526. At what age were you diagnosed with a goiter?
527. What is the full name of the physician who made the diagnosis?
528. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for a goiter.

529. (SINCE YOU TURNED 15 YEARS OF AGE), have you taken thyroid MEDICATION for a goiter?
(If NO, skip to question 530)
529.A. What kind of medication did you take for a goiter?
529.B. How old were you when you **FIRST** took (MEDICATION) for a goiter?
529.C. How old were you when you **LAST** took (MEDICATION) for a goiter?
529.D. What are the names of all of the doctors who have prescribed (MEDICATION) for a goiter?
529.E. May we have your consent to obtain pertinent medical records from your doctor?
529.F. (SINCE AGE 15) have you taken **ANY OTHER** thyroid medication for a goiter?

530. (SINCE AGE 15), have you had thyroid SURGERY for a goiter?
(If NO, skip to question 531)
530.A. How old were you when you had surgery for a goiter?
530.B. What is the name of the hospital where you had thyroid surgery for a goiter?
530.C. May we have your consent to obtain pertinent medical records from the hospital?

531. (SINCE AGE 15), have you had thyroid RADIATION TREATMENT for a goiter?
(If NO, skip to question 532)
531.A. How old were you when you **FIRST** had thyroid radiation treatment for a goiter?
531.B. How old were you when you **LAST** had thyroid radiation treatment for a goiter?
531.C. What are the names of the clinics or hospital where you had radiation treatment for a goiter?
531.D. May we have your consent to obtain pertinent medical records from your doctor?

532. (SINCE AGE 15), have you had ANY OTHER TYPE of thyroid treatment for a goiter?
(If NO, skip to question 533)
532.A. What type of treatment did you have for a goiter?
532.B. How old were you when you **FIRST** had (TREATMENT) for a goiter?
532.C. How old were you when you **LAST** had (TREATMENT) for a goiter?
532.D. What is the name of the doctor who ordered (TREATMENT) for a goiter?
532.E. May we have your consent to obtain pertinent medical records from your doctor?

533. Has a **DOCTOR** ever told you that you had any **OTHER** thyroid problem, other than those we've already talked about?
(If NO, skip to question 542)
534. What type of thyroid problem was it?
535. At what age were you diagnosed with (CONDITION)?
536. What is the full name of the physician who made the diagnosis?
537. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for (CONDITION).

538. (SINCE YOU TURNED 15 YEARS OF AGE) have you taken thyroid MEDICATION for (CONDITION)?
(If NO, skip to question 539)
538.A. What kind of medication did you take for (CONDITION)?
538.B. How old were you when you **FIRST** took (MEDICATION) for (CONDITION)?
538.C. How old were you when you **LAST** took (MEDICATION) for (CONDITION)?
538.D. What are the names of all of the doctors who have prescribed (MEDICATION) for (CONDITION)?
538.E. May we have your consent to obtain pertinent medical records from your doctor?
538.F. (SINCE AGE 15) have you taken any other thyroid medication for (CONDITION)?

539. (SINCE AGE 15), have you had thyroid SURGERY for (CONDITION)?
(If NO, skip to question 540)
539.A. How old were you when you had surgery for (CONDITION)?
539.B. What is the name of the hospital where you had thyroid surgery for (CONDITION)?

539.C. May we have your consent to obtain pertinent medical records from the hospital?

540. (SINCE AGE 15) have you had thyroid RADIATION TREATMENT for (CONDITION)?
(If NO, skip to question 541)
540.A. How old were you when you **FIRST** had thyroid radiation treatment for (CONDITION)?
540.B. How old were you when you **LAST** had thyroid radiation treatment for (CONDITION)?
540.C. What are the names of the clinics or hospital where you had radiation treatment for (CONDITION)?
540.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

541. (SINCE AGE 15) have you had ANY OTHER TYPE of thyroid treatment for (CONDITION)?
(If NO, skip to question 542)
541.A. What type of treatment did you have for (CONDITION)?
541.B. How old were you when you **FIRST** had (TREATMENT) for (CONDITION)?
541.C. How old were you when you **LAST** had (TREATMENT) for (CONDITION)?
541.D. What is the name of the doctor who ordered (TREATMENT) for (CONDITION)?
541.E. May we have your consent to obtain pertinent medical records from your doctor?

542. Has a **DOCTOR** ever given you any thyroid treatment, such as thyroid surgery, radioiodine treatment, thyroid pills or medication, for something **OTHER** than a thyroid problem?
(If NO, skip to quesiton 551)
543. Why did you receive this treatment? ***Record answer***
544. At what age did you receive this treatment?
545. What is the full name of the physician who prescribed this treatment?
546. May we have your consent to obtain pertinent medical records from your doctor?

547. (SINCE YOU TURNED 15 YEARS OF AGE), have you taken thyroid MEDICATION?
(If NO, skip to quesiton 548)
547.A. What kind of medication did you take?
547.B. How old were you when you **FIRST** took (MEDICATION)?
547.C. How old were you when you **LAST** took (MEDICATION)?
547.D. What are the names of all of the doctors who have prescribed (MEDICATION)?
547.E. May we have your consent to obtain pertinent medical records from your doctor?
547.F. (SINCE AGE 15) have you taken any other thyroid medication?

548. (SINCE AGE 15) have you had thyroid SURGERY?
(If NO, skip to question 549)
548.A. How old were you when you had thyroid surgery?
548.B. What is the name of the hospital where you had thyroid surgery?
548.C. May we have your consent to obtain pertinent medical records from the hospital?

549. (SINCE AGE 15) have you had thyroid RADIATION TREATMENT?
(If NO, skip to question 550)
549.A. How old were you when you **FIRST** had thyroid radiation treatment?
549.B. How old were you when you **LAST** had thyroid radiation treatment?
549.C. What are the names of the clinics or hospital where you had radiation treatment?
549.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

550. (SINCE AGE 15) have you had ANY OTHER TPE of thyroid treatment?
(If NO, skip to question 551)
550.A. What type of treatment did you have?
550.B. How old were you when you **FIRST** had (TREATMENT)?
550.C. How old were you when you **LAST** had (TREATMENT)?
550.D. What is the name of the doctor who ordered (TREATMENT)?
550.E. May we have your consent to obtain pertinent medical records from your doctor?

551. Has a doctor ever told you that you had HYPER**PARA**THYROIDISM?
(If NO, skip to question 600)
552. At what age were you diagnosed with hyper**para**thyroidism?
553. What is the full name of the physician who made the diagnosis?
554. May we have your consent to obtain pertinent medical records from your doctor?
555. Have you ever had surgery for hyper**para**thyroidism?
556. What is the name of the hospital where you had parathyroid surgery for hyper**para**thyroidism?
557. May we have your consent to obtain pertinent medical records from the hospital?

SECTION VI: RADIATION TREATMENT
(QXS 600-616)

The next questions are about medical conditions for which you may have had x-ray or radiation treatment.

600. Has a doctor ever told you that you had cancer (**OTHER** than any thyroid cancer you may have already told me about)?
(If NO, skip to question 610)
601. What type of cancer was diagnosed?
602. How old were you when this diagnosis was made?
603. Did you receive radiation treatment for this type of cancer?
604. How old were you when you **FIRST** had radiation treatment?
605. How old were you when you **LAST** had radiation treatment?
606. How many radiation treatments did you have for this cancer?
607. What is the name of the physician who ordered this treatment?
608. May we have your consent to obtain pertinent medical records from your physician?
609. Has a doctor ever told you that you had any other type of cancer?

Next I'll be asking you questions about any radiation or x-ray **TREATMENTS** you may have received to the upper body. ***SHOW CARD 1 - Picture of Upper Body.*** By "upper body" we mean any part of the body that is shaded on this picture. I'm referring only to radiation or x-rays used to **TREAT** a condition, **Not** x-rays used to **DIAGNOSE** problems like broken bones or dental cavities.

I'm only interested in treatments received since you turned 15 years of age.

610. Since age 15, have you had any radiation treatments to the upper body **for acne?**
(If NO, skip to question 611)
610.a. On how many different occasions did you have radiation treatments for acne
610.b. How old were you when you had radiation treatment for acne?
610.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
610.d. What is the full name of the doctor who ordered these treatments?
610.e May we have your consent to obtain pertinent medical records from your doctor?

611. (Since age 15, have you had any radiation treatments to the upper body) **for ring worm?**
(If NO, skip to question 612)
611.a. On how many different occasions did you have radiation treatments for ring worm?
611.b. How old were you when you had radiation treatment for ring worm?
611.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
611.d. What is the full name of the doctor who ordered these treatments?
611.e. May we have your consent to obtain pertinent medical records from your doctor?

612. (Since age 15, have you had any radiation treatments) **for enlarged tonsils?**
(If NO, skip to question 613)

612.a. On how many different occasions did you have radiation treatments for enlarged tonsils?
612.b. How old were you when you had radiation treatment for enlarged tonsils?
612.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
612.d. What is the full name of the doctor who ordered these treatments?
612.e. May we have your consent to obtain pertinent medical records from your doctor?

613. (Since age 15, have you had any radiation treatments to the upper body) **for tuberculosis?**
(If NO, skip to question 614)
613.a. On how many different occasions did you have radiation treatments for tuberculosis?
613.b. How old were you when you had radiation treatment for tuberculosis?
613.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
613.d. What is the full name of the doctor who ordered these treatments?
613.e. May we have your consent to obtain pertinent medical records from your doctor?

614. (Since age 15 have you had any radiation treatments) **for scalp infection?**
(If NO, skip to question 615)
614.a. On how many different occasions did you have radiation treatments for scalp infection?
614.b. How old were you when you had radiation treatment for scalp infection?
614.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
614.d. What is the full name of the doctor who ordered these treatments?
614.e. May we have your consent to obtain pertinent medical records from your doctor?

615. (Since age 15 have you had any radiation treatments) **for enlarged thymus?**
(If NO, skip to question 616)
615.a. On how many different occasions did you have radiation treatments for this condition?
615.b. How old were you when you had radiation treatment for this condition?
615.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
615.d. What is the full name of the doctor who ordered these treatments?
615.e. May we have your consent to obtain pertinent medical records from your doctor?

616. (Since age 15 have you had any radiation treatments to the upper body) **for any other reason?**
(If NO, skip to question 700)
616.a. What was the reason?
616.b. On how many different occasions did you have radiation treatments for (CONDITION)?
616.c. How old were you when you had radiation treatment for (CONDITION)?
616.d. Was a lead shield, such as a collar or apron, usually placed over your neck area?
616.e. What is the full name of the doctor who ordered these treatments?
616.f. May we have your consent to obtain pertinent medical records from your doctor?

SECTION VII: PRESCRIPTION DRUGS

(QXS 700-715)

The next questions are about prescription drugs.

Since you turned 15 years of age, have you ever taken:
For each YES:

700. **Amiodarone or Cordarone?**
(If NO, skip to question 704)
701. **Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.**
702. **Have you taken (MEDICATION) in the last:** 6 months?
703. **How much (MEDICATION) do you take now?**

704. Lithium?
(If NO, skip to question 708)
705. **Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.**
706. **Have you taken (MEDICATION) in the last:** 60 days?
707. **How much (MEDICATION) do you take now?**

708. Dilantin or Tegretol (anti-seizure medication)?
(If NO, skip to question 712)
709. **Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.**
710. **Have you taken (MEDICATION) in the last:** 30 days?
711. **How much (MEDICATION) do you take now?**

712. Glucocorticoids, such as Prednisone or Hydrocortisone?
(If NO, skip to question 800)
713. Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.
714. **Have you taken (MEDICATION) in the last:** 30 days?
715. **How much (MEDICATION) do you take now?**

SECTION VIII: DENTAL X-RAYS
(QXS 800-806)

These last few medical history questions are about routine dental x-rays.

800. Since age 15, have you ever been to a dentist?
(If NO, skip to question 900)
801. Since age 15, have you ever had a dental X-ray?
(If NO, skip to question 900)
802. How old were you when the first x-ray of your teeth was taken? ***If DK, probe for before or after age 15. If over 15, probe for age range.***

We're interested in how often you've had routine dental x-rays and specifically, how these patterns have changed throughout your lifetime.

803. Starting at (AGE 15/AGE IN QX 802/806) how often did you have x-rays taken of your teeth at that time? ***Show Card #2***
804. Was a lead shield (such as an apron or collar) usually placed over the neck area?
805. Did the frequency of having dental x-rays (QX 803) ever change, or did the use of a lead shield ever change?
806. How old were you when this pattern changed?

SECTION IX: DEMOGRAPHICS
(QXS 900-914)

Now I would like to ask some questions about you and your background. If you choose not to answer any one of the questions simply tell me and we will move on to the next question. You may end the interview at any time.

900. Overall how accurate do you think you were able to be in answering the questions in this interview? ***SHOW CARD #3***

901. **Question Deleted**
902. **Question Deleted**
903. **Question Deleted**
904. What is your current marital status? ***SHOW CARD #4***
905. What is the highest grade or level you attended in school? ***SHOW CARD #5***
906. What race or ethnic origin do you consider yourself to be? ***SHOW CARD #6***
(If NATIVE AMERICAN, ask questions 907 through 909)
(If HISPANIC, skip to question 911)
(Otherwise, skip to question 910)
907. What is your Native American ancestry?
908. Are you an enrolled member of a Federally recognized Tribe or Nation?
909. Which Tribe or Nation?
910. Are you of Spanish or Hispanic Origin?
(If NO, skip to question 912)
911. What is your Hispanic origin? ***SHOW CARD #7***
912. What is your religious preference? ***SHOW CARD #8***
913. Last year at this time, how many people, including yourself, were living in your household?
914. In (YEAR BEFORE INTERVIEW DATE), what was your combined household yearly income before taxes? ***SHOW CARD #9***

SECTION X. FAMILIARITY
(QX 1000-1007)

Finally, I would like to ask you a few miscellaneous questions.

1000. What, if anything, do you feel contributes to a person developing thyroid disease?
1001. Please tell me all the types of health problems, if any, you feel may be caused by radiation released from Hanford?
1002. How knowledgeable do you think you are about radiation released from Hanford?
1003. **Question deleted**
1004. Do you believe the health of anyone in your family has been affected by radiation from Hanford?
1005. Do you have any comments you would like to add?
1006. We will send you copies of the results from your complete diagnostic evaluation for thyroid disease and if any results are not normal, we will call you. ***(Check consent form for permission to contact personal physician)***

If no permission:

You indicated on your consent form that you do not want us to contact your personal physician, therefore we will not call or send results to your doctor.

If permission given:

You indicated on your consent form that we can send all results to your personal doctor. Do you have your doctor's complete mailing address? [If you call our office by next Friday with your doctor's complete mailing address and phone number, we can send a copy of your results to him or her.]

1007. Would you like to be put on the study's mailing list to receive regular updates of the study's progress?

If you have medical records consent forms from CATI for the subject to sign:

I have (NUMBER) additional medical records consent forms that I would like you to sign. These are requests for medical records relating to your medical history before age 15, which was reported by the person you identified for the telephone interview.

CLOSING COMMENTS FOR THE RESPONDENT WHO HAS YET TO HAVE A PHYSICAL EXAM:

I want to thank you very much for your cooperation. You're now scheduled to have a blood sample collected. I'll go check to see if _____ is ready for you at the next station. I'll come back in a moment to get you. ***(Check to see if next station is ready)*** Thank you again for participating in our study.

TIME INTERVIEW ENDED: ____ ____ : ____ ____ A.M./P.M.

SECTION XI - INTERVIEWER COMMENTS
(QXS 1100-1103)

1100. Respondent's cooperation was:
1101. The quality of the respondent's response was:
(If HIGH QUALITY or GENERALLY RELIABLE, skip to question 1103)
1102. What is the main reason for the unreliable or questionable quality of the interview?
1103. Did the respondent sign consent form giving us permission to request records from (HIS/HER) physician(s)?

IN-PERSON QUESTIONNAIRE - EXPANDED VERSION

HANFORD THYROID DISEASE STUDY

PHASE	INITIALS	DATE
EDITED		
CODED		
KEYED		
VERIFIED		

\+ = use continuation page

SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __

TIME BEGUN: __ __ : __ __ A.M. / P.M.

QUESTIONNAIRE VERSION #: 12/11/95 06

INTERVIEWER ID: _____

BIRTHDATE (MM/DD/YY) : __ __ / __ __ / __ __

CLINIC LOCATION: _____

CLINIC CODE ___ ___

DATE OF INTERVIEW: ___ ___ / ___ ___ / ___ ___

INTERVIEW OUTCOME: ___

1 = COMPLETE
2 = PARTIAL COMPLETE

FORM APPROVED: OMB NUMBER: 0920-0296
EXP. DATE: May 31, 1998

My name is (INTERVIEWER'S NAME). I'm one of the interviewers for the Hanford Thyroid Disease Study. I'll be asking you some questions about your residential, medical, and occupational history, along with some other questions. Before we begin this interview, there are a few things I need to mention:

* All of the information you provide will be kept strictly confidential as required by public law PHS Act Section 308(d)(42 USC 242m(d)).
* Try to be as accurate as possible when answering the questions. Don't feel rushed, and do not hesitate to ask me to repeat a question.
* If you choose not to answer a question, simply tell me and we will move on to the next question.
* You may end the interview at any time.

Do you have any questions before we begin? *(Answer questions)* My job as the interviewer is to read the questions exactly as they are written. For this reason, please wait until after I've read the complete question before giving me your answer.

SECTION I: RESIDENCE HISTORY

Part 1: Mother's Residence History
(QXS 1-5)

YES *(birthdate is 12/01/44 or later)*
NO *(birthdate is before 12/01/44)*

I'd like to begin by asking you questions about the places where your mother lived while she was pregnant with you. This would be her residences between ____ / ____ and ____ / ____ . If you have the interview preparation worksheet, please refer to it for this section.

1. Starting in (____ / ____) , what town did your mother live in?
   Or (WHAT TOWN/WHERE) did your mother move to in (QX 5)?
2. What (STATE/COUNTRY) is that in?
3. What county is that in?
   If outside study area, skip to QX 5.
4. What was her street address or location?
5. What month and year did your mother move (FROM RESIDENCE/OUT OF COUNTY)?
   If date moved is after subject's birthdate, enter subject's birthdate and skip to Subject's Residence section (Question 6). If date moved is before subject's birthdate, enter the date moved and continue with the mother's residence history (repeat from Question 1).

Part 2: Subject's Residence History: Birth-1957
(QXS 6-14)

The (first/next) questions I'll be asking you are about the places where you have lived from birth through 1957. [If you have the interview preparation worksheet, please refer to it for this section.] In some instances I will also ask about the types of milk you drank and dairy products you ate. Let's start with where your family lived when you were born.

6. What town did you live in when you were born?
   Or (WHAT TOWN/WHERE) did you move to in (QX 10)?
7. What (STATE/COUNTRY) is that in?
8. What county is that in?
   If outside study area, skip to QX 10
9. What was your street address or location?
10. What month and year did you move (FROM RESIDENCE/OUT OF COUNTY)?*
    ** If date is after 12/31/57, ask QXs 11-14 if in study area, then skip to Part 3 (Question 100)*
11. From (RESIDENCE START DATE) to (RESIDENCE LAST DATE/DECEMBER 1957), did you ever eat or drink fresh milk or dairy products made from raw cow's milk?
12. During this time, did you ever eat or drink fresh milk or dairy products made from processed cow's milk?
13. During this time, did you ever eat or drink fresh milk or dairy products made from raw goat's milk?
14. During this time, did you ever eat or drink fresh milk or dairy products made from processed goat's milk?
    Repeat from Question 6 until December 1957

Part 3: Subject's Residence History: 1958-Present

(QXS 100-115)

The next questions I'll be asking are about some places you may have lived between January 1, 1958 and the present.

For each YES answer, ask Questions 111-115
If NO or DON'T KNOW, ask next question or skip to Question 200

100. Since 1958, have you lived in Nevada?
101. Since 1958, have you lived in Utah?
102. Since 1958, have you lived in Arizona?
103. Since 1958, have you lived in New Mexico?
104. Since 1958, have you lived in Colorado?
105. Since 1958, have you lived in Idaho?
106. Since 1958, have you lived in Ohio?
107. Since 1958, have you lived in South Carolina?
108. Since 1958, have you lived in Tennessee?
109. Did you live in the Marshall Islands at anytime in 1958, or 1959?
110. Did you live in Pennsylvania at anytime in 1979?

111. Enter 2-digit state abbreviation

112. What county did you live in?
If county not known, ask: What town did you live in?
113. In what month and year did you (first/next) move to (County/City) in (State)?
114. In what month and year did you (first/next) move out of (County/City) in (State)?
115. Did you ever live in (State) at any other time?

Repeat Questions 112-115 for each residence in each state of interest; then continue with Question 200.

SECTION II: OCCUPATIONAL HISTORY
(QXS 200-212)

Now I'm going to ask you some questions about your employment history.

200. Have you ever worked in any of the following industries or occupations?
(For each YES, ask questions 201-210)
    a. Geology?
    b. Metallurgy?
    c. Metal Processing?
    d. Ore Refining?
    e. Mining?
    f. In the nuclear industry, as a civilian?
    g. On the premises of a nuclear facility?
    h. In health care, with exposure to radioactive materials or x-rays?
    i. As a scientist, Researcher, or Student with exposure to radioactive materials or x-rays?
    j. In the military, working around nuclear testing, nuclear submarines, or other radiation exposure?
    k. Have you worked in any other industry or occupation where you may have been exposed to radioactive materials or x-rays?

201. What was the name of the company or organization you worked for?

Interviewer: Skip to QX 203 if same field

202. Have you already told me about this particular job?
203. In which city and state was your job?
204. What did this company or organization make or do?
205. What was your job title there?
206. What were your activities and duties as (JOB TITLE)?
207. When did you start there as a (JOB TITLE)?
208. When did you last work there as a (JOB TITLE)?
209. Was that full-time or part-time employment?
210. Have you ever worked in any other jobs in (SAME FIELD)?
If YES, repeat from Question 202
If NO or DON'T KNOW, skip to Question 211

211. What have been your primary occupations?
212. Other than through medical tests or procedures, have you EVER been exposed to any radiation that you know of?

SECTION III - SMOKING HISTORY
(QXS 300-321)

I'm going to ask you about smoking and tobacco use. The first series of questions is about cigarette use, and is divided into two parts. The first will ask about NON-FILTER cigarettes only, and the second will ask about FILTER cigarettes.

300. Have you ever smoked a total of 100 or more NON-FILTER cigarettes in your lifetime?
301. At what age did you (FIRST/NEXT) start smoking non-filter cigarettes?
302. Did you ever stop smoking non-filter cigarettes for six consecutive months or longer?
303a. How old were you when you (FIRST/NEXT) stopped smoking non-filter cigarettes?
304a. On the average, how many non-filter cigarettes did you smoke per day between age (QX 301) and age (QX 303a)?
305a. Did you ever start smoking non-filter cigarettes again?
303b. What is your current age?
304b. On the average, how many non-filter cigarettes have you smoked per day since age (QX 301)?
306. Have you ever smoked a total of 100 or more FILTER cigarettes in your lifetime?
307. At what age did you (FIRST/NEXT) start smoking filter cigarettes?
308. Did you ever stop smoking filter cigarettes for six consecutive months or longer?
309a. How old were you when you (FIRST/NEXT) stopped smoking filter cigarettes?
310a. On the average, how many filter cigarettes did you smoke per day between age (QX 307) and age (QX 309a)?
311a. Did you ever start smoking filter cigarettes again?
309b. What is your current age?
310b. On the average, how many filter cigarettes have you smoked per day since age (QX 307)?

The next questions are about smoking cigars and tobacco pipes.

312. Have you ever smoked CIGARS on a regular basis for six months or longer?
313. How old were you when you first started smoking cigars?
314. How old were you when you last smoked cigars?
315. From age (QX 313) to age (QX 314), how many total years did you smoke cigars?
316. How many would you usually smoke in a week?
317. Have you ever smoked tobacco in a PIPE on a regular basis for six months or longer?

318. How old were you when you first started smoking a pipe?
319. How old were you when you last smoked a pipe?
320. From age (QX 318) to age (QX 319), how many total years did you smoke a pipe?
321. How many bowls would you usually smoke in a week?

SECTION IV - DIAGNOSTIC MEDICAL PROCEDURES
(QXS 400-459)

The next set of questions is about DIAGNOSTIC medical procedures you may have had. I'll be asking you specific questions about different types of medical tests. If you don't understand a question, please let me know and I'll explain the procedure I'm asking about.

DIAGNOSTIC X-RAYS
(QXS 400-443)

First I'll be asking about radiologic procedures taken to diagnose a problem or condition of the upper body. I'm now referring to X-rays and CAT scans taken to diagnose broken bones or other conditions, not including routine dental
X-rays. I'm only interested in diagnostic procedures you've had to the shaded portion of the body shown in the picture. *Show Card 1*.

400. Have you ever had a CAT scan of your upper body?
If YES, ask Questions 401-405
If NO or DON'T KNOW, skip to Question 406
401. Why was a CAT scan performed?
402. What area was scanned?
403. How many CAT scans were performed?
404. How old were you when you (first) had a CAT scan for (REASON)?
405. Did you ever have a CAT scan of your upper body for any other reason?
If YES, repeat from Question 401
If NO or DON'T KNOW, skip to Question 406

406. Have you ever had any diagnostic x-rays taken of your HEAD? Now this would include head x-rays taken for orthodontic work and oral surgery, but would NOT include routine dental x-rays.
If YES, ask Questions 407-411
If NO or DON'T KNOW, skip to Question 412
407. Why was an x-ray taken?
408. On how many occasions were x-rays taken of your HEAD for (REASON)?
409. How old were you when you (first) had an x-ray taken of your HEAD for (REASON)?
410. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
411. Was an x-ray of your HEAD ever taken for any other reason?
If YES, repeat from Question 407
If NO or DON'T KNOW, go to Question 412

412. Have you ever had any diagnostic x-rays taken of your NECK?
If YES, ask Questions 413-416
If NO or DON'T KNOW, skip to Question 417
413. Why was an x-ray taken?
414. On how many occasions were x-rays taken of your NECK for (REASON)?
415. How old were you when you (first) had a NECK x-ray taken for (REASON)?
416. Was an x-ray of your NECK ever taken for any other reason?

If YES, repeat from Question 413
If NO or DON'T KNOW, skip to Question 417

417. Have you ever had any diagnostic x-rays taken of your CHEST or UPPER BACK (including mammograms)?
If YES, ask Questions 418-422
If NO or DON'T KNOW, skip to Question 423
418. Why was an x-ray taken?
419. On how many occasions were x-rays taken of your CHEST or UPPER BACK for (REASON)?
420. How old were you when you (first) had an x-ray taken for (REASON)?
421. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
422. Was an x-ray of your CHEST OR UPPER BACK (including mammograms) ever taken for any other reason?
If YES, repeat from Question 418
If NO or DON'T KNOW, skip to Question 423

423. Have you ever had any diagnostic x-rays taken of your STOMACH OR MID-BACK?
If YES, ask Questions 424-428
If NO or DON'T KNOW, skip to Question 429
424. Why was an x-ray taken?
425. On how many occasions were x-rays taken of your STOMACH OR MID-BACK for (REASON)?
426. How old were you when you (first) had an x-ray taken for (REASON)?
427. Was a lead shield (such as a collar or apron) usually placed over your NECK when you had (this x-ray/these x-rays)?
428. Was an x-ray of your STOMACH OR MID-BACK ever taken for any other reason?
If YES, repeat from Question 424
If NO or DON'T KNOW, skip to Question 429

FLUOROSCOPIES
(QXS 429-449)

Fluoroscopy is a type of x-ray in which certain parts of the body are observed on a fluorescent screen, like a TV set. The doctor can view various parts of the body by watching the screen. A dye is sometimes used, and may be swallowed or injected into a vein. Fluoroscopy is used in a number of diagnostic procedures. I will ask you if you have had some procedures performed on the UPPER part of the body as shown in the picture. I will also ask about barium enemas.

429. Have you ever had a BARIUM ENEMA?
If YES, ask Questions 430-433
If NO or DON'T KNOW, skip to Question 434
430. Why did you have a Barium Enema?
431. How many Barium Enemas did you have for (REASON)?
432. How old were you when you (first) had a Barium Enema for (REASON)?
433. Was a Barium Enema ever done for any other reason?
If YES, repeat from Question 430
If NO or DON'T KNOW, skip to Question 434

434. Have you ever had an UPPER GI?
If YES, ask Questions 435-438
If NO or DON'T KNOW, skip to Question 439
435. Why did you have an Upper GI?

436. How many Upper GIs did you have for (REASON)?
437. How old were you when you (first) had an Upper GI for (REASON)?

438. Was an Upper GI ever done for any other reason?
If YES, repeat from Question 435
If NO or DON'T KNOW, skip to Question 439

439. Have you ever had an INTRAVENOUS PYELOGRAM or IVP?
If YES, ask Questions 440-443
If NO or DON'T KNOW, skip to Question 444
440. Why did you have an IVP?
441. How many IVPs did you have for (REASON)?
442. How old were you when you (first) had an IVP for (REASON)?
443. Was an IVP ever done for any other reason?
If YES, repeat from Question 440
If NO or DON'T KNOW, skip to Question 444

444. Did you ever have any other fluoroscopies of your upper body?
If YES, ask Questions 445-449
If NO or DON'T KNOW, skip to Question 450
445. What part of the upper body?
446. Why did you have a fluoroscopy?
447. How many fluoroscopies did you have for (REASON)?
448. How old were you when you (first) had a fluoroscopy for (REASON)?
449. Was a fluoroscopy ever taken for any other reason?
If YES, repeat from Question 445
If NO or DON'T KNOW, skip to Question 450

THYROID SCANS AND OTHER NUCLEAR MEDICINE PROCEDURES
(QXS 450-458)

The next few questions are about diagnostic nuclear medicine procedures. These are sometimes called "scans". During these procedures, a radioactive substance is given by mouth or injected into a vein to make an area of the body show up on an x-ray in order to diagnose a medical problem.

450. Have you ever had a thyroid nuclear scan?
If YES, ask Questions 451-454
If NO or DON'T KNOW, skip to Question 455
451. In what month and year did you have this thyroid nuclear scan?
452. What is the name of the physician who requested this thyroid nuclear scan?
453. May we have your consent to obtain pertinent medical records from your physician?
454. Did you have any other thyroid nuclear scans?
If YES, repeat from Question 451
If NO or DON'T KNOW, skip to Question 455

455. Have you ever had any other NUCLEAR SCANS? (that is, a procedure in which a radioactive substance is given by mouth or injected into a vein to diagnose a medical problem?)
If YES, ask Questions 456-459
If NO or DON'T KNOW, skip to Question 500
456. What type of procedure was done?
457. Why was this procedure done?
458. In what month and year did you have this procedure?
459. Have you had any other nuclear scans?

If YES, repeat from Question 456
If NO or DON'T KNOW, skip to Question 500

SECTION V: THYROID PROBLEMS
(QXS 500-557)

The next set of questions is about thyroid disease. If you don't understand a question, please let me know and I'll describe the condition I'm asking about.

500. Has a DOCTOR ever told you that you had GRAVES' DISEASE or hyperthyroidism, that is, an OVER-active thyroid?
If YES, ask Questions 501-507
If NO or DON'T KNOW, skip to Question 508
501. At what age were you diagnosed with Graves' disease or over-active thyroid?
502. What is the full name of the physician who diagnosed this condition?
503. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for Graves' Disease or over-active thyroid.

504. Have you taken THYROID MEDICATION for Graves' Disease or an over-active thyroid?
If YES, ask Questions 504A-504F
If NO or DON'T KNOW, skip to Question 505
504.A. What kind of medication did you take for this condition?
504.B. How old were you when you FIRST took (MEDICATION) for over-active thyroid?
504.C. How old were you when you LAST took (MEDICATION) for this condition?
504.D. What are the names of all of the doctors who have prescribed (MEDICATION) for this condition?
504.E. May we have your consent to obtain pertinent medical records from your doctor?
504.F. Have you taken ANY OTHER thyroid medication for Graves' disease or an over-active thyroid?
If YES, repeat from Question 504A
If NO or DON'T KNOW, skip to Question 505

505. Have you had THYROID SURGERY for Graves' Disease or over-active thyroid?
If YES, ask Questions 505A-505C
If NO or DON'T KNOW, skip to Question 506
505.A. How old were you when you had thyroid surgery for this condition?
505.B. What is the name of the hospital where you had this thyroid surgery?
505.C. May we have your consent to obtain pertinent medical records from the hospital?

506. Have you had THYROID RADIATION TREATMENT for Graves' Disease or over-active thyroid?
If YES, ask Questions 506A-506D
If NO or DON'T KNOW, skip to Question 507
506.A. How old were you when you FIRST had thyroid radiation treatment for this condition?
506.B. How old were you when you LAST had thyroid radiation treatment for this condition?
506.C. What are the names of the clinics or hospitals where you had this radiation treatment?
506.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

507. Have you had ANY OTHER TYPE of thyroid treatment for Graves' Disease or over-active thyroid?
If YES, ask Questions 507A-507E
If NO or DON'T KNOW, skip to Question 508
507.A. What type of treatment did you have for this condition?
507.B. How old were you when you FIRST had (TREATMENT) for this condition?
507.C. How old were you when you LAST had (TREATMENT) for this condition?

507.D. What is the name of the doctor who ordered (TREATMENT)?
507.E. May we have your consent to obtain pertinent medical records from your doctor?

508. Has a DOCTOR ever told you that you were hypothyroid, that is, had an UNDER-active thyroid?
If YES, ask Questions 509-515
If NO or DON'T KNOW, skip to Question 516

509. At what age were you diagnosed with an under-active thyroid?
510. What is the full name of the physician who diagnosed this condition?
511. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for an under-active thyroid.

512. Have you taken THYROID MEDICATION for an under active thyroid?
If YES, ask Questions 512A-512F
If NO or DON'T KNOW, skip to Question 513
512.A. What kind of medication did you take for under-active thyroid?
512.B. How old were you when you FIRST took (MEDICATION) for under-active thyroid?
512.C. How old were you when you LAST took (MEDICATION) for under-active thyroid?
512.D. What are the names of all of the doctors who have prescribed (MEDICATION) for under-active thyroid?
512.E. May we have your consent to obtain pertinent medical records from your doctor?
512.F. Have you taken ANY OTHER thyroid medication for an under-active thyroid?
If YES, repeat from Question 512A
If NO or DON'T KNOW, skip to Question 513

513. Have you had THYROID SURGERY for under-active thyroid?
If YES, ask Questions 513A-513C
If NO or DON'T KNOW, skip to Question 514
513.A. How old were you when you had thyroid surgery for under-active thyroid?
513.B. What is the name of the hospital where you had thyroid surgery for under-active thyroid?
513.C. May we have your consent to obtain pertinent medical records from this hospital?

514. Have you had THYROID RADIATION TREATMENT for under-active thyroid?
If YES, ask Questions 514A-514E
If NO or DON'T KNOW, skip to Question 515
514.A. How old were you when you FIRST had thyroid radiation treatment for under-active thyroid?
514.B. How old were you when you LAST had thyroid radiation treatment for under-active thyroid?
514.C. What are the names of the clinics or hospital where you had radiation treatment for under active thyroid?
514.E. May we have your consent to obtain pertinent medical records from the clinic or hospital?

515. Have you had ANY OTHER TYPE of thyroid treatment for under-active thyroid?
If YES, ask Questions 515A-515E
If NO or DON'T KNOW, skip to Question 516
515.A. What type of treatment did you have for under-active thyroid?
515.B. How old were you when you FIRST had (TREATMENT) for under-active thyroid?
515.C. How old were you when you LAST had (TREATMENT) for under-active thyroid?
515.D. What is the name of the doctor who ordered (TREATMENT) for under-active thyroid?
515.E. May we have your consent to obtain pertinent medical records from your doctor?

516. Has a DOCTOR ever told you that you had a THYROID NODULE or TUMOR?

If YES, ask Questions 517-524
If NO or DON'T KNOW, skip to Question 525

517. Was this thyroid nodule or tumor benign or malignant?
518. At what age were you diagnosed with a thyroid (CONDITION)?
519. What are the full names of the physicians who diagnosed this condition?
520. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for a thyroid (CONDITION).

521. Have you taken thyroid MEDICATION for a thyroid (CONDITION)?
If YES, ask Questions 521A-521F
If NO or DON'T KNOW, skip to Question 522
521.A. What kind of medication did you take for a thyroid (CONDITION)?
521.B. How old were you when you FIRST took (MEDICATION) for a thyroid (CONDITION)?
521.C. How old were you when you LAST took (MEDICATION) for a thyroid (CONDITION)?
521.D. What are the names of all of the doctors who have prescribed (MEDICATION) for a thyroid (CONDITION)?
521.E. May we have your consent to obtain pertinent medical records from your doctor?
521.F. Have you taken any other thyroid medication for a thyroid (CONDITION)?
If YES, repeat from Question 521A
If NO or DON'T KNOW, skip to Question 522

522. Have you had thyroid SURGERY for a thyroid (CONDITION)?
If YES, ask Questions 522A-522C
If NO or DON'T KNOW, skip to Question 523
522.A. How old were you when you had surgery for thyroid (CONDITION)?
522.B. What is the name of the hospital where you had thyroid surgery for thyroid (CONDITION)?
522.C. May we have your consent to obtain pertinent medical records from the hospital?

523. Have you had thyroid RADIATION TREATMENT for thyroid (CONDITION)?
If YES, ask Questions 523A-523D
If NO or DON'T KNOW, skip to Question 524
523.A. How old were you when you FIRST had thyroid radiation treatment for thyroid (CONDITION)?
523.B. How old were you when you LAST had thyroid radiation treatment for thyroid (CONDITION)?
523.C. What are the names of the clinics or hospital where you had radiation treatment for thyroid (CONDITION)?
523.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

524. Have you had ANY OTHER TYPE of thyroid treatment for thyroid (CONDITION)?
If YES, ask Questions 524A-524E
If NO or DON'T KNOW, skip to Question 525
524.A. What type of treatment did you have for thyroid (CONDITION)?
524.B. How old were you when you FIRST had (TREATMENT) for thyroid (CONDITION)?
524.C. How old were you when you LAST had (TREATMENT) for thyroid (CONDITION)?
524.D. What is the name of the doctor who ordered (TREATMENT) for thyroid (CONDITION)?
524.E. May we have your consent to obtain pertinent medical records from your doctor?

525. Has a DOCTOR ever told you that you had a GOITER?
If YES, ask Questions 526-532
If NO or DON'T KNOW, skip to Question 534
526. At what age were you diagnosed with a goiter?
527. What is the full name of the physician who made the diagnosis?

528. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for a goiter.

529. Have you taken thyroid MEDICATION for a goiter?
If YES, ask Questions 529A-529F
If NO or DON'T KNOW, skip to Question 530
529.A. What kind of medication did you take for a goiter?
529.B. How old were you when you FIRST took (MEDICATION) for a goiter?
529.C. How old were you when you LAST took (MEDICATION) for a goiter?
529.D. What are the names of all of the doctors who have prescribed (MEDICATION) for a goiter?
529.E. May we have your consent to obtain pertinent medical records from your doctor?
529.F. Have you taken ANY OTHER thyroid medication for a goiter?
If YES, repeat from Question 529A
If NO or DON'T KNOW, skip to Question 530

530. Have you had thyroid SURGERY for a goiter?
If YES, ask Questions 530A-530C
If NO or DON'T KNOW, skip to Question 531
530.A. How old were you when you had surgery for a goiter?
530.B. What is the name of the hospital where you had thyroid surgery for a goiter?
530.C. May we have your consent to obtain pertinent medical records from the hospital?

531. Have you had thyroid RADIATION TREATMENT for a goiter?
If YES, ask Questions 531A-531D
If NO or DON'T KNOW, skip to Question 532
531.A. How old were you when you FIRST had thyroid radiation treatment for a goiter?
531.B. How old were you when you LAST had thyroid radiation treatment for a goiter?
531.C. What are the names of the clinics or hospital where you had radiation treatment for a goiter?
531.D. May we have your consent to obtain pertinent medical records from your doctor?

532. Have you had ANY OTHER TYPE of thyroid treatment for a goiter?
If YES, ask Questions 532A-532E
If NO or DON'T KNOW, skip to Question 533
532.A. What type of treatment did you have for a goiter?
532.B. How old were you when you FIRST had (TREATMENT) for a goiter?
532.C. How old were you when you LAST had (TREATMENT) for a goiter?
532.D. What is the name of the doctor who ordered (TREATMENT) for a goiter?
532.E. May we have your consent to obtain pertinent medical records from your doctor?

533. Has a DOCTOR ever told you that you had any OTHER thyroid problem, other than those we've already talked about?
If YES, ask Questions 534-541
If NO or DON'T KNOW, skip to Question 542
534. What type of thyroid problem was it?
535. At what age were you diagnosed with (CONDITION)?
536. What is the full name of the physician who made the diagnosis?
537. May we have your consent to obtain pertinent medical records from your doctor?

Now I'd like to ask about the different types of treatment you may have had for (CONDITION).

538. Have you taken thyroid MEDICATION for (CONDITION)?
If YES, ask Questions 538A-538F
If NO or DON'T KNOW, skip to Question 539
538.A. What kind of medication did you take for (CONDITION)?

538.B. How old were you when you FIRST took (MEDICATION) for (CONDITION)?
538.C. How old were you when you LAST took (MEDICATION) for (CONDITION)?
538.D. What are the names of all of the doctors who have prescribed (MEDICATION) for (CONDITION)?
538.E. May we have your consent to obtain pertinent medical records from your doctor?
538.F. Have you taken any other thyroid medication for (CONDITION)?

539. Have you had thyroid SURGERY for (CONDITION)?
If YES, ask Questions 539A-539C
If NO or DON'T KNOW, skip to Question 540
539.A. How old were you when you had surgery for (CONDITION)?
539.B. What is the name of the hospital where you had thyroid surgery for (CONDITION)?
539.C. May we have your consent to obtain pertinent medical records from the hospital?

540. Have you had thyroid RADIATION TREATMENT for (CONDITION)?
540.A. How old were you when you FIRST had thyroid radiation treatment for (CONDITION)?
540.B. How old were you when you LAST had thyroid radiation treatment for (CONDITION)?
540.C. What are the names of the clinics or hospital where you had radiation treatment for (CONDITION)?
540.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

541. Have you had ANY OTHER TYPE of thyroid treatment for (CONDITION)?
If YES, ask Questions 541A-541E
If NO or DON'T KNOW, skip to Question 542
541.A. What type of treatment did you have for (CONDITION)?
541.B. How old were you when you FIRST had (TREATMENT) for (CONDITION)?
541.C. How old were you when you LAST had (TREATMENT) for (CONDITION)?
541.D. What is the name of the doctor who ordered (TREATMENT) for (CONDITION)?
541.E. May we have your consent to obtain pertinent medical records from your doctor?

542. Has a DOCTOR ever given you any thyroid treatment, such as thyroid surgery, radioiodine treatment, thyroid pills or medication, for something OTHER than a thyroid problem?
If YES, ask Questions 543-550
If NO or DON'T KNOW, skip to Question 551

543. Why did you receive this treatment?
544. At what age did you receive this treatment?
545. What is the full name of the physician who prescribed this treatment?
546. May we have your consent to obtain pertinent medical records from your doctor?

547. Have you taken thyroid MEDICATION?
If YES, ask Questions 547A-547F
If NO or DON'T KNOW, skip to Question 548
547.A. What kind of medication did you take?
547.B. How old were you when you FIRST took (MEDICATION)?
547.C. How old were you when you LAST took (MEDICATION)?
547.D. What are the names of all of the doctors who have prescribed (MEDICATION)?
547.E. May we have your consent to obtain pertinent medical records from your doctor?
547.F. Have you taken any other thyroid medication?

If YES, repeat from Question 547A
If NO or DON'T KNOW, skip to Question 548

548. Have you had thyroid SURGERY?
If YES, ask Questions 548A-548C
If NO or DON'T KNOW, skip to Question 549
548.A. How old were you when you had thyroid surgery?
548.B. What is the name of the hospital where you had thyroid surgery?
548.C. May we have your consent to obtain pertinent medical records from the hospital?

549. Have you had thyroid RADIATION TREATMENT?
If YES, ask Questions 549A-549D
If NO or DON'T KNOW, skip to Question 550
549.A. How old were you when you FIRST had thyroid radiation treatment?
549.B. How old were you when you LAST had thyroid radiation treatment?
549.C. What are the names of the clinics or hospital where you had radiation treatment?
549.D. May we have your consent to obtain pertinent medical records from the clinic or hospital?

550. Have you had ANY OTHER TYPE of thyroid treatment?
If YES, ask Questions 550A-550E
550.A. What type of treatment did you have?
550.B. How old were you when you FIRST had (TREATMENT)?
550.C. How old were you when you LAST had (TREATMENT)?
550.D. What is the name of the doctor who ordered (TREATMENT)?
550.E. May we have your consent to obtain pertinent medical records from your doctor?

551. Has a doctor ever told you that you had HYPERPARATHYROIDISM?
If YES, ask Question 552-557
If NO or DON'T KNOW, skip to Question 600

552. At what age were you diagnosed with hyperparathyroidism?
553. What is the full name of the physician who made the diagnosis?
554. May we have your consent to obtain pertinent medical records from your doctor?

555. Have you ever had surgery for hyperparathyroidism?
If YES, ask Questions 556-557
If NO or DON'T KNOW, skip to Question 600

556. What is the name of the hospital where you had parathyroid surgery for hyperparathyroidism?
557. May we have your consent to obtain pertinent medical records from the hospital?

SECTION VI: RADIATION TREATMENT
(QXS 600-616)

The next questions are about medical conditions for which you may have had x-ray or radiation treatment.

600. Has a doctor ever told you that you had cancer (OTHER than any thyroid cancer you may have already told me about)?
If YES, ask Questions 601-609
If NO or DON'T KNOW, skip to Question 610

601. What type of cancer was diagnosed?
If YES, ask Questions 602-609
If NO or DON'T KNOW, skip to Question 610
602. How old were you when this diagnosis was made?
603. Did you receive radiation treatment for this type of cancer?
604. How old were you when you FIRST had radiation treatment?
605. How old were you when you LAST had radiation treatment?
606. How many radiation treatments did you have for this cancer?
607. What is the name of the physician who ordered this treatment?
608. May we have your consent to obtain pertinent medical records from your physician?
609. Has a doctor ever told you that you had any other type of cancer?
If YES, repeat from Question 601
If NO or DON'T KNOW, skip to Question 610

Next I'll be asking you questions about any radiation or x-ray TREATMENTS you may have received to the upper body. *SHOW CARD 1 - Picture of Upper Body.* By "upper body" we mean any part of the body that is shaded on this picture. I'm referring only to radiation or x-rays used to TREAT a condition, Not x-rays used to DIAGNOSE problems like broken bones or dental cavities.

610. Have you ever had any radiation treatments to the upper body for acne?
If YES, ask Questions 610A-610E
If NO or DON'T KNOW, skip to Question 611
610.a. On how many different occasions did you have radiation treatments for acne?
610.b. How old were you when you had radiation treatment for acne?
610.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
610.d. What is the full name of the doctor who ordered these treatments?
610.e May we have your consent to obtain pertinent medical records from your doctor?

611. (Have you ever had any radiation treatments to the upper body) for ring worm?
If YES, ask Questions 611A-611E
If NO or DON'T KNOW, skip to Question 612
611.a. On how many different occasions did you have radiation treatments for ring worm?
611.b. How old were you when you had radiation treatment for ring worm?
611.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
611.d. What is the full name of the doctor who ordered these treatments?
611.e. May we have your consent to obtain pertinent medical records from your doctor?

612. (Have you ever had any radiation treatments) for enlarged tonsils?
If YES, ask Questions 612A-612E
If NO or DON'T KNOW, skip to Question 613
612.a. On how many different occasions did you have radiation treatments for enlarged tonsils?
612.b. How old were you when you had radiation treatment for enlarged tonsils?
612.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
612.d. What is the full name of the doctor who ordered these treatments?
612.e. May we have your consent to obtain pertinent medical records from your doctor?

613. (Have you ever had any radiation treatments to the upper body) for tuberculosis?
If YES, ask Question 613A-613E
If NO or DON'T KNOW, skip to Question 614
613.a. On how many different occasions did you have radiation treatments for tuberculosis?
613.b. How old were you when you had radiation treatment for tuberculosis?
613.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
613.d. What is the full name of the doctor who ordered these treatments?

613.e. May we have your consent to obtain pertinent medical records from your doctor?

614. (Have you ever had any radiation treatments) for scalp infection?
If YES, ask Questions 614A-614E
If NO or DON'T KNOW, skip to Question 615
614.a. On how many different occasions did you have radiation treatments for scalp infection?
614.b. How old were you when you had radiation treatment for scalp infection?
614.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
614.d. What is the full name of the doctor who ordered these treatments?
614.e. May we have your consent to obtain pertinent medical records from your doctor?

615. (Have you ever had any radiation treatments) for enlarged thymus?
If YES, ask Questions 615A-616E
If NO or DON'T KNOW, skip to Question 616
615.a. On how many different occasions did you have radiation treatments for this condition?
615.b. How old were you when you had radiation treatment for this condition?
615.c. Was a lead shield, such as a collar or apron, usually placed over your neck area?
615.d. What is the full name of the doctor who ordered these treatments?
615.e. May we have your consent to obtain pertinent medical records from your doctor?

616. (Have you ever had any radiation treatments to the upper body) for any other reason?
If YES, ask Questions 616A-616E
If NO or DON'T KNOW, skip to Question 700
616.a. What was the reason?
616.b. On how many different occasions did you have radiation treatments for (CONDITION)?
616.c. How old were you when you had radiation treatment for (CONDITION)?
616.d. Was a lead shield, such as a collar or apron, usually placed over your neck area?
616.e. What is the full name of the doctor who ordered these treatments?
616.f. May we have your consent to obtain pertinent medical records from your doctor?

SECTION VII: PRESCRIPTION DRUGS
(QXS 700-715)

The next questions are about prescription drugs.

700. Have you ever taken Amiodarone or Cordarone?
If YES, ask Questions 701-703
If NO or DON'T KNOW, skip to Question 704
701. Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.
702. Have you taken (MEDICATION) in the last 6 months?
703. How much (MEDICATION) do you take now?

704. Have you ever taken Lithium?
If YES, ask Questions 705-707
If NO or DON'T KNOW, skip to Question 708
705. Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.
706. Have you taken (MEDICATION) in the last 60 days?
707. How much (MEDICATION) do you take now?

708. Have you ever taken Dilantin or Tegretol (anti-seizure medication)?
If YES, ask Questions 709-711
If NO or DON'T KNOW, skip to Question 612

709. Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.
710. Have you taken (MEDICATION) in the last 30 days?
711. How much (MEDICATION) do you take now?

712. Have you ever taken Glucocorticoids, such as Prednisone or Hydrocortisone?
If YES, ask Questions 713-715
If NO or DON'T KNOW, skip to Question 800
713. Starting with when you first took (MEDICATION), please tell me during what time periods you have taken this medication.
714. Have you taken (MEDICATION) in the last 30 days?
715. How much (MEDICATION) do you take now?

SECTION VIII: DENTAL X-RAYS
(QXS 800-806)

These last few medical history questions are about routine dental x-rays.

800. Have you ever been to a dentist?
If YES, ask Question 801
If NO or DON'T KNOW, skip to Question 900

801. Have you ever had a dental X-ray?
If YES, ask Questions 801-806
If NO or DON'T KNOW, skip to Question 900

802. How old were you when the first x-ray of your teeth was taken?

We're interested in how often you've had routine dental x-rays and specifically, how these patterns have changed throughout your lifetime.

803. Starting at (AGE IN QX 802/806) how often did you have x-rays taken of your teeth at that time?
804. Was a lead shield (such as an apron or collar) usually placed over the neck area?
805. Did the frequency of having dental x-rays (QX 803) ever change, or did the use of a lead shield ever change?
If YES, ask Question 806 then repeat from Question 803
If NO or DON'T KNOW, skip to Question 900
806. How old were you when this pattern changed?

SECTION IX: DEMOGRAPHICS
(QXS 900-914)

Now I would like to ask some questions about you and your background. If you choose not to answer any one of the questions simply tell me and we will move on to the next question. You may end the interview at any time.

900. Overall how accurate do you think you were able to be in answering the questions in this interview? ***SHOW CARD #3***
901. **Question Deleted**
902. **Question Deleted**
903. **Question Deleted**

904. What is your current marital status? ***SHOW CARD #4***
905. What is the highest grade or level you attended in school? ***SHOW CARD #5***
906. What race or ethnic origin do you consider yourself to be? ***SHOW CARD #6***
(If NATIVE AMERICAN, ask questions 907 through 909)
(If HISPANIC, skip to question 911)
(Otherwise, skip to question 910)
907. What is your Native American ancestry?
908. Are you an enrolled member of a Federally recognized Tribe or Nation?
909. Which Tribe or Nation?
910. Are you of Spanish or Hispanic Origin?
(If NO, skip to question 912)
911. What is your Hispanic origin? ***SHOW CARD #7***
912. What is your religious preference? ***SHOW CARD #8***
913. Last year at this time, how many people, including yourself, were living in your household?
914. In (YEAR BEFORE INTERVIEW DATE), what was your combined household yearly income before taxes? ***SHOW CARD #9***

SECTION X. FAMILIARITY
(QX 1000-1007)

Finally, I would like to ask you a few miscellaneous questions.

1000. What, if anything, do you feel contributes to a person developing thyroid disease?
1001. Please tell me all the types of health problems, if any, you feel may be caused by radiation released from Hanford?
1002. How knowledgeable do you think you are about radiation released from Hanford?
1003. **Question deleted**
1004. Do you believe the health of anyone in your family has been affected by radiation from Hanford?
1005. Do you have any comments you would like to add?
1006. We will send you copies of the results from your complete diagnostic evaluation for thyroid disease and if any results are not normal, we will call you. ***(Check consent form for permission to contact personal physician)***

If no permission:
You indicated on your consent form that you do not want us to contact your personal physician, therefore we will not call or send results to your doctor.

If permission given:
You indicated on your consent form that we can send all results to your personal doctor. Do you have your doctor's complete mailing address? [If you call our office by next Friday with your doctor's complete mailing address and phone number, we can send a copy of your results to him or her.]

1007. Would you like to be put on the study's mailing list to receive regular updates of the study's progress?

CLOSING COMMENTS FOR THE RESPONDENT WHO HAS YET TO HAVE A PHYSICAL EXAM:

I want to thank you very much for your cooperation. You're now scheduled to have a blood sample collected. I'll go check to see if _____ is ready for you at the next station. I'll come back in a moment to get you. ***(Check to see if next station is ready)*** Thank you again for participating in our study.

TIME INTERVIEW ENDED: ____ ____ : ____ ____ A.M./P.M.

SECTION XI - INTERVIEWER COMMENTS
(QXS 1100-1103)

1100. Respondent's cooperation was:
1101. The quality of the respondent's response was:
(If HIGH QUALITY or GENERALLY RELIABLE, skip to question 1103)
1102. What is the main reason for the unreliable or questionable quality of the interview?
1103. Did the respondent sign consent form giving us permission to request records from (HIS/HER) physician(s)?

INTERVIEW PREPARATION WORKSHEET

Please take a few minutes to write down the following information and bring it with you to your clinic appointment. You can refer to these pages during your interview. This will help us to complete the interview more quickly and accurately.

Between January 1, 1958 and the present, have you ever lived in any of the following states:

	please circle
Nevada	Yes / No
Utah	Yes / No
Arizona	Yes / No
New Mexico	Yes / No
Colorado	Yes / No
Idaho	Yes / No
Ohio	Yes / No
South Carolina	Yes / No
Tennessee	Yes / No
Did you live in the Marshall Islands anytime in 1958 or 1959?	Yes / No
Did you live in Pennsylvania anytime during 1979?	Yes / No

If you answered "yes" to any of the locations listed above, please indicate the STATE, the COUNTY (or CITY, if the county is unknown) and the DATES you lived in each county in the space below.

STATE: _____ COUNTY: _____ CITY: _____
(if county unknown)

FROM: _____ / _____ TO: _____ / _____
month year month year

STATE: _____ COUNTY: _____ CITY: _____
(if county unknown)

FROM: _____ / _____ TO: _____ / _____
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

STATE: ____________________ COUNTY: ____________________ CITY: ____________
(if county unknown)

FROM: ______ / ______ TO: ______ / ______
month year month year

If you need more space, please use a separate sheet of paper.

PERSONAL DOCTORS:

Please list the names and addresses of doctors who have treated you for any type of **thyroid disease**.

If you need additional space, use the back of this page or a separate sheet of paper.

Name _____
Address _____
City/State/Zip _____
Phone _____

Name _____
Address _____
City/State/Zip _____
Phone _____

Name _____
Address _____
City/State/Zip _____
Phone _____

Name _____
Address _____
City/State/Zip _____
Phone _____

Name _____
Address _____
City/State/Zip _____
Phone _____

DOCTOR/PRESCRIPTION MEDICATIONS LIST

It is our policy to send copies of your test results from the HTDS clinic to you. If you would also like us to send copies of the results to your personal health care provider, please write in your health care provider's complete address in the space below.

Provider's Name _____

Address _____

_____

City/State/Zip _____

Phone _____

PRESCRIPTION MEDICATIONS:

Please list any prescription medications you have taken in the last 30 days and the daily dosage.

MEDICATION	**DOSAGE**
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

HANFORD THYROID DISEASE STUDY

FINAL DIAGNOSIS DETERMINATION FORM

SUBJECT ID #: __ __ __ __ __ __ __ __ __ __ __	DATE OF DIAGNOSIS:___ ___ / ___ ___ / ___ ___
[1] BENIGN THYROID NODULE	
[ ] YES **[ ] NO** **[ ] UNKNOWN**	BASIS FOR DIAGNOSIS: *(Circle **One**)* 1..... HISTOLOGIC DIAGNOSIS, HTDS 2.....CYTOLOGIC DIAGNOSIS, HTDS 3.....HISTOLOGIC DIAGNOSIS, PRIOR 4.....CYTOLOGIC DIAGNOSIS, PRIOR 5.....CLINICAL DIAGNOSIS, HTDS 6.....CLINICAL DIAGNOSIS, PRIOR 7.....PARTICIPANT/RESPONDENT REPORT ONLY
COMMENT:	check if diagnosis incidental from nuclear scans [ ]
	histologic/cytologic type: *(Circle **All** That Apply)* 1 .....colloid nodule 2 .....follicular adenoma 3 .....other, specify: _____

[2] THYROID CARCINOMA

[ ] YES
[ ] NO
[ ] UNKNOWN

comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 histologic diagnosis, htds
2 cytologic diagnosis, htds
3 histologic diagnosis, prior
4 cytologic diagnosis, prior
5 clinical diagnosis, htds
6 clinical diagnosis, prior
7 participant/respondent report only

_____SUBJECT I.D.: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

HANFORD THYROID DISEASE STUDY

CAUSE OF DEATH FORM

1. DATE OF BIRTH: ___ ___ / ___ ___ / ___ ___ (M/D/Y)

2. DATE OF DEATH: ___ ___ / ___ ___ / ___ ___ (M/D/Y)

3. AGE AT DEATH: ___ ___

4. CAUSE OF DEATH:

PREMATURITY 1
CONGENITAL DISEASE (SPECIFY) 2
_____
TRAUMA 3
INFECTIOUS DISEASE 4
CANCER (SPECIFY) 5
_____
CARDIOVASCULAR DISEASE 6
OTHER (SPECIFY) 7
_____
DK 9

5. WAS THIS DEATH RELATED TO THYROID OR PARATHYROID DISEASE?.....

YES 1
NO .....2 (SKIP TO QX 6)
DK .....9 (SKIP TO QX 6)

_____ THYROID CARCINOMA

_____ HYPOTHYROIDISM

_____ HYPERTHYROIDISM

_____ HYPERPARATHYROIDISM

CODES:

PRIMARY CAUSE 1
CONTRIBUTED 2
DID NOT CONTRIBUTE 3
UNKNOWN WHETHER CONTRIBUTED 4
DISEASE NEVER PRESENT 5

6. SOURCES FOR CAUSE OF DEATH INFORMATION:

	SOURCE AVAILABLE?	THYROID DISEASE REFERENCED?
A. AUTOPSY REPORT	YES.....1	YES.....1
	NO.....2	NO.....2
B. DEATH CERTIFICATE	YES.....1	YES.....1
	NO.....2	NO.....2
C. MEDICAL RECORDS	YES.....1	YES.....1
(Other than autopsy report)	NO.....2	NO.....2
D. DOSIMETRY QUESTIONNAIRE	YES.....1	YES.....1
	NO.....2	NO.....2
E. OTHER (SPECIFY)	YES.....1	YES.....1
_____	.....NO	2.....NO
2		

check if diagnosis incidental from nuclear scans [ ]
histologic/cytologic type: (Circle Only One)

1 papillary carcinoma
2 follicular carcinoma
3 mixed follicular-papillary carcinoma
4 medullary carcinoma
5 anaplastic carcinoma
6 other, specify: _____

[3] THYROID NODULE SUSPICIOUS FOR MALIGNANCY

[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 histologic diagnosis, htds
2 cytologic diagnosis, htds
3 histologic diagnosis, prior
4 cytologic diagnosis, prior
5 clinical diagnosis, htds
6 clinical diagnosis, prior
7 participant/respondent report only
check if diagnosis incidental from nuclear scans [ ]
[4] SIMPLE GOITER
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 participant/respondent report only
etiology of goiter: (Circle All That Apply)
1 graves' disease
2 hashimoto's thyroiditis
3 hypothyroidism, nos
4 hyperthyroidism, nos
5 other, specify: _____
[5] MULTINODULAR THYROID GLAND
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 participant/respondent report only
check if diagnosis incidental from nuclear scans [ ]
etiology of multinodular thyroid gland:
(Circle All That Apply)
1 graves' disease
2 hashimoto's thyroiditis
3 hypothyroidism, nos
4 hyperthyroidism, nos
5 other, specify: _____
[6] AUTOIMMUNE THYROIDITIS (HASHIMOTO'S THYROIDITIS)
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 participant/respondent report only
[7] GRAVES' DISEASE
[ ] YES
[ ] NO
[ ] UNKNOWN

comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 participant/respondent report only
[8] HYPOTHYROIDISM
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 inferred from past/current therapy
5 participant/respondent report only
if basis=2, enter lab values that document the diagnosis
(N/A = Not Available)
tsh: _____ range of normal: (ll) _____ (UL) _____
fti: _____ range of normal: (ll) _____ (UL) _____
possible contributing causes: (Circle All That Apply)
1 no
2 yes (indicate all that apply)
1 i-131 therapy
2 thyroid/parathyroid surgery
3 lithium therapy
4 other, specify: _____
[9] HYPERTHYROIDISM
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 inferred from past/current therapy
5 participant/respondent report only
if basis=2, enter lab values that document the diagnosis
(N/A = Not Available)
tsh: _____ range of normal: (ll) _____ (UL) _____
fti: _____ range of normal: (ll) _____ (UL) _____
etiology of hyperthyroidism: (Circle All That Apply)
1 graves' disease
2 toxic nodular goiter
3 solitary autonomous nodule
4 subacute thyroiditis
5 silent/post-partum thyroiditis
6 exogenous thyroid medication
7 uncertain
8 other, specify: _____
[10] OTHER THYROID DISEASE

[ ] YES (Specify: _____)
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
2 medical record with supporting documentation
3 medical record without supporting documentation
4 inferred from past/current therapy
5 participant/respondent report only
[11] HYPERPARATHYROIDISM
[ ] YES
[ ] NO
[ ] UNKNOWN
comment:
BASIS FOR DIAGNOSIS: (Circle One)
1 htds evaluation
(Elevated serum calcium and parathyroid hormone levels with or without low serum phosphate levels)
2 medical record with supporting documentation
3 medical record without supporting documentation
4 participant/respondent report only
GENERAL COMMENTS

[12] HTDS ULTRASOUND FINDINGS
Circle All That Apply:
1 palpable ultrasound detected nodules
2 nonpalpable focal ultrasound detected abnormalities
3 diffuse ultrasound detected abnormalities
4 normal
5 gland not visualized
comment:
[13] PALPABLE NODULES NOT DETECTED BY HTDS ULTRASOUND
Circle One:
1 yes
2 no
3 uncertain
comment:
DATA FORM COMPLETED: ____ PHYSICIAN ID: ____ ____
DATE KEY ENTERED: __ __ / __ __ / __ __ KEY ENTRY I.D. #: __ __ 7/28/95

PNWD-3060

Responses to National Academy of Sciences Review Comments on Dosimetry in the Fred Hutchinson Cancer Research Center's Hanford Thyroid Disease Study

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Paul Eslinger
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September 2000

Letter report for the
Fred Hutchinson Cancer Research Center

Battelle Pacific Northwest Laboratories
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Responses to National Academy of Sciences Review Comments on Dosimetry in the Fred Hutchinson Cancer Research Center's Hanford Thyroid Disease Study

Introduction

Battelle Northwest staff cognizant of the Hanford Environmental Dose Reconstruction (HEDR) Project at Battelle was asked to assist researchers at Fred Hutchinson Cancer Research Center (FHCRC) in responding to radiation-dosimetry-related issues raised during a recent National Academy of Sciences review of the Hanford Thyroid Disease Study Draft Final Report.

Battelle staff performing the HEDR Project, under contract to the Centers for Disease Control and Prevention (CDC), developed computer data sets and codes for use in calculating doses to individuals who lived in the vicinity of the Hanford Site in the 1940's and 1950's. A sequence of codes (STRM, RATCHET, and DESCARTES) was utilized to develop the data set for use in the code that computes individual doses (CIDER) (Ouderkirk and Eslinger 1993; Eslinger et al. 1994). The FHCRC, also under contract to CDC, used the HEDR database and CIDER code to estimate radiation doses for the subjects in the Hanford Thyroid Disease Study. The HTDS draft results were presented in a Draft Final Report, which was reviewed at CDC's request by the National Academy of Sciences *Committee on an Assessment of Centers for Disease Control and Prevention Radiation Studies from DOE Contractor Sites, Subcommittee to Review the Hanford Thyroid Disease Study Results and Final Report*. The NAS committee had several questions and made a number of comments, some of which were directed at the dosimetric methods derived from the HEDR codes. Specific issues raised in NAS' Section 4, Evaluation of Dosimetric Methods, include:

- Impact of errors in validation of ^{131}I on pasture grass on individual dose estimates,
- Sensitivity of deposition estimates to selection of wind field representation,
- Validity of consultant F.O. Hoffman's assertion of underestimation of source term,
- Values for intake of milk cattle feed and forage,
- Milk cow feed-to-milk transfer coefficient,
- Impact of errors in the use of dry-to-wet ratios in the validation efforts,
- Enhancement of the library of fetal dose conversion factors,
- Statistical independence of individual dose conversion factors within and across stochastic representations, and
- Accounting for uncertainty in HTDS individual survey responses.

Overview of Report

In order to respond to the NAS comments, they were organized and grouped into related topics, roughly parallel to the list of issues described above. Each of these topics is essentially

independent of the others, and each may be considered separately. Each section of this report addresses a particular topic or group of topics.

Section 1 of the report addresses comments in the National Academy of Sciences Letter Report regarding earlier discussions on the impact of errors introduced in the report *Validation of HEDR Models* (Napier et al. 1994). This section incorporates the first and sixth issues above, since they are directly related. A great deal of this effort had been completed in prior work related to iodine/sagebrush modeling; the pertinent results are abstracted and related directly to the NAS comments.

Section 2 of the report discusses evaluation of the inverse-square wind field model implemented in the RATCHET code. This section incorporates responses to the second issue above. The selection of the inverse-square approach was extensively documented in early HEDR Project reports and public discussions, specifically J.V. Ramsdell, Jr., 1992, *Summary of the March 25-26, 1991 Atmospheric Model Working Meeting*, PNWD-1975 HEDR and J.V. Ramsdell, Jr., and E.D. Skyllingstad, 1993, *A Review of Wind Field Models for Atmospheric Transport*, PNWD-2148 HEDR. It is apparent that these reports were not available for the NAS review. The results of this prior effort have been abstracted and related directly to the NAS comments.

Section 3 of the report addresses assertions of underestimation of iodine releases in later years (1950s and 1960s). This section incorporates responses to the third issue above. Monthly and quarterly reports of historical Hanford stack monitoring results are available. Monitoring for individual processing plant stacks (i.e., B-Plant, T-Plant, REDOX, and PUREX) is available, the monthly stack monitoring values do differ from the Heeb model (STRM), but the aggregate sums by month are relatively close to the Heeb totals. Additional sources of monitoring data are also compared to the HEDR estimates.

Section 4 documents the final milk cow feeding regimes used in the HEDR DESCARTES data files as directed by the HEDR Technical Steering Panel (TSP). This section addresses the fourth issue. The TSP directed the final selection of the 4 commercial and 4 back-yard-cow feeding regimes currently available in the CIDER database. The feeding regimes were not specifically documented in any reports issued by the HEDR Project. The input requirements from the TSP, the TSP's own report on the subject (Price 1994), and the DESCARTES input data files are available. The feeding regimes used are described in detail.

Section 5 addresses milk-cow feed-to-milk transfer coefficients, the fifth issue above. The relationship of the various available data sets on the parameter F_m, the feed-to-milk transfer coefficient, was discussed in one of the last HEDR Project public meetings in Seattle. That information was not available to the NAS for their review. External reviewers and the public extensively discussed the subject in that meeting. The information behind that presentation has been reconstructed and related directly to the NAS comments.

Section 6 addresses issue number 7 above, the fetal dose conversion factor file for CIDER. When the HEDR files were turned over to CDC for use by FHCRC, the file containing dose conversion factors for the prenatal period contained a simplistic default value (Snyder et al. 1994). FHCRC desired to replace that distribution with a more realistic one. The file was recreated with the appropriate distribution and supplied to FHCRC and CDC.

Section 7 describes minor modifications to the CIDER code. These modifications were made to address the last two NAS issues. One set of modifications allows randomization of the order of selection of stochastic dose conversion factors. The CIDER code as originally designed performed no stochastic variable selection; all realizations of all parameters were input from externally-created files. This was done for simplicity in CIDER and for repeatability of the calculations. Following discussions with the FHCRC scientists, a random selection algorithm was developed to permute the inputs. A second set of modifications provided subject-specific stochastic inputs to the CIDER code to account for potential uncertainties in the individual food consumption interview results. Inputs are now either generic and stochastic, by way of Reference Diet files, individual-specific and deterministic by way of direct data input, or new combinations of the two options. A set of algorithms for assigning uncertainty to the interview data was developed; these are described.

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Snyder, S.F., W.T. Farris, B.A. Napier, T.A. Ikenberry, and R.O. Gilbert. 1994. Parameters Used in the Environmental Pathways and Radiological Dose Modules (DESCARTES, CIDER, and CRD) of the Hanford Environmental Dose Reconstruction Integrated Codes (HEDRIC). PNWD-2023 HEDR Rev. 1, Battelle Pacific Northwest Laboratories, Richland, Washington

1. Validation of HEDR models

The National Academy of Sciences review of the HTDS dosimetry included a request that "the HEDR investigators supplement their description of the model with an account of the origin of errors made with regard to the estimation of ^{131}I concentrations in pasture grass on the basis of measurements, the impact on the predicted values when the errors are corrected, and a preliminary assessment of the effect of reparameterization on estimates of absorbed dose to the thyroid." This call came in response to presentations made to the NAS committee by HEDR staff pointing out errors that had been discovered in certain portions of the model validation work reported in Napier et al (1994). These errors included omission of the wet-to-dry conversion factor for sagebrush in the comparison of calculated (dry) sagebrush concentrations and measured (wet) sagebrush concentrations. A second error was the use of an incorrect value in the conversion of counting rates to concentration for the 1949 data, caused when an early draft of a supporting report was used without updating when the final value was published.

The initial results of validation testing of the environmental radiation dosimetry models developed for the Hanford Environmental Dose Reconstruction Project were published in Napier et al. (1994), *Validation of HEDR Models*. Most recently, some minor errors have been identified in certain of the validation attempts published in Napier et al. The first set of errors discovered in the published HEDR validation involves the omission of the wet-to-dry conversion factor for sagebrush in the modeling. The most likely maximum value for the wet-to-dry factor is 2 grams wet/gram dry, evaluated over the course of one year by measurements by the author. However, sagebrush growth is acclimated for the annual precipitation pattern, in which nearly half of the annual rainfall occurs in the winter months. There is significant leaf drop in July and August, the period when the original model indicates highest biomass. Since the sagebrush is not in the human or animal food chain and is just a dead end in the model, these difficulties did not have any impact on the final dose calculations. However, developing a better sagebrush model, particularly the interception portions, and repeating the validation attempts provides strong support for the remainder of the HEDR modeling and the individual radiation dose calculations that use them.

The second error involves the conversion of counts per minute, as recorded in 1949 for the sagebrush samples, to estimated concentration in vegetation. The published results used a conversion factor to get from counts to concentration of 0.0017. The conversion

factor for 1949 described in Denham, Mart, and Thiede (1993) is reported to be 0.0044. The records pertaining to the preparation of Denham, Mart, and Thiede (1993) were retrieved from the Hanford records center and the history of the document was reviewed. The conversion factor was revised from 0.0017 to 0.0044 during the document s final preparation. The conversion factor is a simple product of a constant, the measurement factor M, and the yield factor Y. The yield used is 63 percent (0.63). The yield factor Y is defined as the reciprocal of the yield. In the early drafts, the conversion factor is equal to the constant times M times the yield. In the later report, the conversion factor is equal to the constant times M times the yield factor Y. It is apparent that the early drafts had a simple mathematical error that was fixed prior to the document's issuance. Application of the correct conversion factor would tend to increase the measured concentrations by a factor of about 2.5.

Consideration of the errors together indicate that the concentrations of iodine-131 in sagebrush predicted by the HEDR models tend to be uniformly low by about a factor of 3. While it is possible that either the source term estimate or the atmospheric dispersion/deposition modeling is low by this amount, it can be shown that either of these possibilities is remote. It is most likely that the sagebrush model itself imposes a bias. The model used was a simple one, and for expediency used the same formulation as the vegetable models in the HEDR codes (Ikenberry et al. 1991). The benefit of this model was that the quotient (interception fraction/ biomass) was essentially a constant over time. However, the total interception fraction predicted by this model is always less than 15%. This model uses a sinusoidal plant growth curve - that is known to be not appropriate for sagebrush. It also uses the Chamberlain filtration model to get to interception fraction - and the standard range for that, too. Either or both of those could be inappropriate for sagebrush.

A complete revision to the sagebrush model in the HEDR DESCARTES code was implemented. The results are described below. The results were submitted for peer review, and accepted for publication in the journal *Environmental Radioactivity*. The following sections are the paper that was submitted; a slightly shorter version (omitting the Green Run portion for brevity) was accepted for publication. The article will be published as:

Napier, B.A., P.W. Eslinger, W.E. Nichols, and L. Anderlini. 2000. "Improvements in Modeling Sagebrush Concentrations of Radioactive Iodine Released from the Hanford Site," *Environmental Radioactivity*.

1.1 Background

In 1987, the U.S. Department of Energy directed the Pacific Northwest Laboratory, operated by Battelle Memorial Institute, to conduct the Hanford Environmental Dose Reconstruction (HEDR) Project. The purpose of the HEDR Project was to estimate the radiation dose that individuals could have received as a result of emissions of radioactive materials from the Hanford Site in the south-central part of Washington State.

The HEDR Project determined that ^{131}I in an airborne pathway was the dominant radionuclide in the dose received by most individuals living near the Hanford Site. A series of models and computer codes were developed by the HEDR Project to reconstruct the movement of iodine from the reactors and processing plants through the atmosphere, in the food chain, and finally resulting in dose to humans (Heeb, Gydesen, Simpson, & Bates, 1996; Ramsdell, Simonen, Burk, & Stage, 1996; Farris, Napier, Ikenberry, & Shipler, 1996). Eventually, the modeling domain for dose estimation was expanded to cover a 200,000 km^2 (75,000 square mile) region including parts of the states of Washington, Oregon, and Idaho (Shipler, Napier, Farris, & Freshley, 1996). Figure 1-1 contains a map showing the location of the Hanford site.

A measure of uncertainty was desired for the dose estimates, and was obtained by running 100 model replications in a stochastic framework. Each model replication utilized randomized values for a large number of input variables. Most of the parameters were selected using a Latin Hypercube scheme. Details on the randomized variables are provided in Snyder, Farris, Napier, Ikenberry & Gilbert (1994).

A series of validation studies on the HEDR models relative to historical sampling data are reported by Napier, Simpson, Eslinger, Ramsdell, Thiede, & Walters (1994). One validation study for deposition of ^{131}I on sagebrush (*Artemisia tridentata*) indicated that the simulation models systematically underestimated historical sampled data during the cold weather months of 1946. This lack of agreement prompted development of a revised model for deposition of airborne ^{131}I on sagebrush.

Because of the historical nature of the data, the original activity units (curies and picocuries) have been retained for reporting the results in this work.

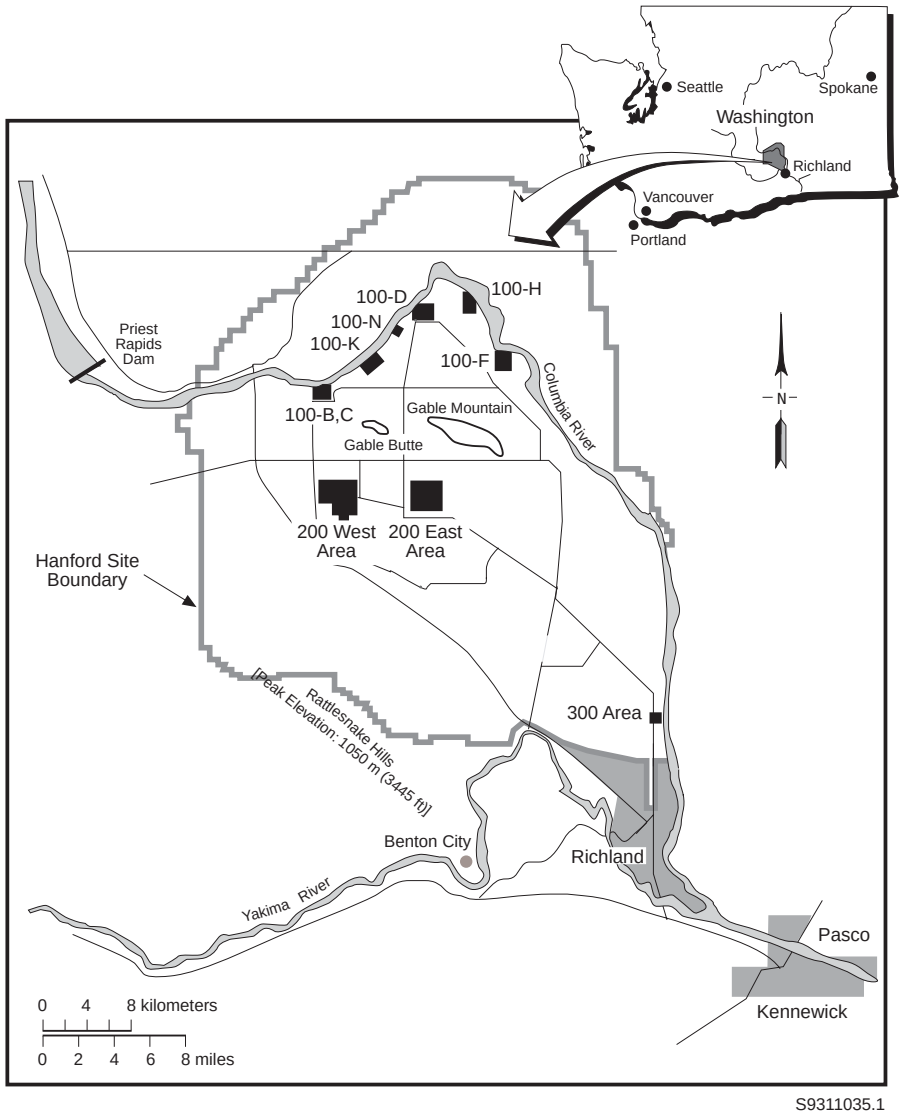

Figure 1-1. Map showing the location of the Hanford Site.

1.2 Derivation of the Concentration Model

The traditional approach to determining deposition and retention of an airborne radioactive material on vegetation uses the following equation:

$$C_{plant} = C_{air}\ V_d\ \frac{r}{B}\ \frac{(1 - e^{-(\lambda_r + \lambda_w)\,t})}{(\lambda_r + \lambda_w)}$$

where

C_{plant} = the concentration of radionuclide on the plant surface, Bq/g,
C_{air} = the assumed steady-state concentration of radionuclide in air, Bq/m^3,
V_d = a transfer coefficient termed the "deposition velocity" because of its units, m/s,
r = the fraction of deposited material intercepted by the vegetation, unitless,
B = the above-ground biomass of the vegetation, g,
λ_r = the radiological decay constant, s^{-1}, and
λ_w = the weathering removal constant, s^{-1}.
t = time, s

This equation assumes constant average air concentrations, and for constant air concentration the plant concentration builds up over time to a steady-state, equilibrium value on the vegetation surface. The equation was developed for a conceptual model of microscopic particles drifting downward (the product $C_{air}\ V_d$ can be thought of as a downward flux of material, Bq/m^2 s), being filtered from the air with a fractional interception by plant leaves (the interception fraction r).

A minor modification of this approach considers deposition and/or interception as an equilibrium process between air and plant surface. This conceptual model is more appropriate for gaseous iodine (I_2). The partitioning is driven by concentration and, as discussed below, may be a function of temperature. This approach is described for semi-volatile organic materials by Komp and McLachlen (1997), and adapted for iodine here.

The conceptual model involves rate constants for deposition of iodine onto plant leaves and revolatilization, and includes decay and "weathering." Weathering addresses loss of radioactive material from the plant by means other than volatilization (such as leaf drop, rainoff, growth dilution, etc., as typically described in the radioecological literature). The differential equation describing this process is

$$\frac{dQ_{plant}}{dt} = K_{a/p}\, C_{air} - (\lambda_r + \lambda_w + K_{p/a})\, Q_{plant}$$

where

Q_{plant} = quantity of radionuclide on the plant, (Bq),
$K_{a/p}$ = transfer coefficient from the air to the plant, (m/s),
$K_{p/a}$ = transfer coefficient from the plant surface back to the air, (m/s).

In this derivation, the transfer from the air to the leaves is the product $K_{a/p}\, C_{air}$ and the revolatilization is the product $K_{p/a}\, Q_{plant}$. C_{air} is assumed constant for the time period in question, therefore, the equation can be written in terms of air concentration rather than a time varying air quantity. The solution to this equation is

$$Q_{plant} = K_{a/p}\, C_{air}\, \frac{(1 - e^{-(K_{p/a} + \lambda_r + \lambda_w)t})}{(K_{p/a} + \lambda_r + \lambda_w)}$$

Recognizing that $Q_{plant} = B\, C_{plant}$, this equation can be rewritten as

$$C_{plant} = K_{a/p}\, C_{air}\, \frac{(1 - e^{-(K_{p/a} + \lambda_r + \lambda_w)t})}{B\,(K_{p/a} + \lambda_r + \lambda_w)}$$

Note the similarities between this solution and that of the traditional method. The revolatilization rate constant $K_{p/a}$ is thought to be small since there is little evidence of radioiodine rapidly devolving from samples, and if it is much smaller than radioactive decay it can be neglected. The terms $K_{a/p}$ and $V_d r$ are then roughly functionally equivalent; the gas deposition rate constant is essentially the deposition velocity and interception fraction combined. Because the absolute value of $K_{a/p}$ must be estimated from available data, it is specific to the vegetation type used in the estimation. The advantage to the traditional formulation is that the interception term, r, allows the general formula to be applied to many types of vegetation.

1.3 Calibration Data for the Concentration Model

The absolute value of $K_{p/a}$ for sagebrush may be estimated from data presented in Soldat (1965). Soldat presents the results of monitoring air and sagebrush near the Hanford Site following an acute release of ^{131}I in 1963. Soldat's measurements are presented in Table

Table 1-1. Derivation of $K_{a/p}$ using Sagebrush and Air Concentration Data Collected by Soldat in 1963.

Concentration				
Sagebrush (pCi/g)	Air (pCi/m^3)	Days exposed	Derived $K_{a/p}$ (m/d)	Comment
6.5	0.85	9	14.73	sage stems
0.7	0.7	9	1.93	
0.09	0.35	2	1.47	
0.38	0.28	2	7.75	
0.1	0.32	2	1.78	
14	2.3	2	34.76	
91	52.6	1	18.50	most applicable
125	72.7	1	18.39	most applicable
			1.4 to 34.8	Range of data
			18.5	Best estimate

1-1. The release occurred following a series of continuous smaller releases, thus the largest depositions and air concentrations probably have the least interference with pre-existing concentrations. A subset of Soldat's data was used in calibrating $K_{p/a}$ because air concentrations and sagebrush concentrations taken at the same time were needed.

In order to estimate the values of $K_{a/p}$, the biomass of the sagebrush must be estimated. The data of Soldat (1965) were collected in early September; it is assumed that sagebrush were in a summer dormant period with a minimal dry biomass of about 10 g/m^2. The half-life for ^{131}I is 8.05 days. Estimates of $K_{a/p}$ derived from the C_{plant} equation are given in Table 1-1. The numerical values are derived assuming that $K_{p/a}$ is negligible and the weathering half-time is 14 days (Snyder, Farris, Napier, Ikenberry, & Gilbert, 1994). The best estimate of $K_{a/p}$ (based on the largest measured values and the time closest to the deposition event) is about 18.5 m/d and the range is from 1.4 to 35 m/d. The estimate for bare sage stems is not significantly different than for leafy sage. This implies that the biomass estimate for the sage should not have a major influence on the concentration estimate.

For a nominal dry biomass of 50 g/m^2 and an interception fraction of about 0.15 used by HEDR (Snyder et al. 1994), the value of $K_{a/p}$ of 18.5 m/d is equivalent to a deposition velocity of about 0.0014 m/s. This is about equal to the large-area average

deposition velocity of 0.002 m/s produced using the HEDR atmospheric dispersion and deposition computer code RATCHET (Ramsdell et al., 1996; Ramsdell, et al., 1994). This agreement implies that the mass balance required for proper operation of RATCHET is being maintained.

The values of $K_{a/p}$ in Table 1-1 are all derived for conditions in September 1963. The average monthly temperature in September 1963 was 21.7 degrees (71.1 degrees Fahrenheit) (Hoitink & Burk, 1998). Monthly average temperatures at Hanford typically range from –1 to 24 degrees C (30 to 75 degrees F), with monthly averages in exceptional years dropping as low as -12 or as high as 27 degrees C (10 to 80 degrees F). It is theoretically anticipated that the gas driven rate constant should vary with temperature. Komp & McLachlan (1997) present an integrated van't Hoff equation that provides a means based on thermodynamics for expressing the temperature dependence:

$$K_{a/p}(T) = K_{a/p}(T_{ref}) \exp\left[\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\frac{\Delta H}{R}\right]$$

where

- T = the absolute temperature of interest, degree Kelvin,
- T_{ref} = a reference absolute temperature, i.e., that for which data are available, degree Kelvin
- ΔH = the enthalpy of phase change between the plant and the air, J/mole, and
- R = the ideal gas constant, J/degree mole.

It is suggested by McLachlan, Welsch-Pausch, & Tolls (1995) that the enthalpy of vaporization can be used for ΔH, which is the equivalent to assuming that the temperature dependence of $K_{a/p}$ is the same as the temperature dependence of the vapor pressure of the material. This makes physical sense and corresponds with the assumptions used in the derivation of the deposition equation of gas-plant equilibrium. The work of Komp & McLachlan (1997) and McLachlan et al. (1995) explicitly addresses semivolatile organic liquids such as PCBs, but it also appears applicable to semivolatile gases such as iodine. For iodine, the numerical value of ΔH for the solid/gas transition is 14.88 kcal/g mole (62,300 J/mole) (Chemical Rubber Co. 1974). The numerical value for R is 8.314 J/degree mole (Rosenbaum 1970).

Table 1-2. Temperature Dependence of $K_{a/p}$ for Sagebrush for $\Delta H_f = 62{,}300$.

Temperature		
F	K	$K_{a/p}$ (m/d)
10	261	504.0
20	266	276.7
30	272	155.7
40	277	89.7
50	283	52.8
60	289	31.7
70	294	19.4
71	295	18.5
80	300	12.1

Using the best-estimate value of $K_{a/p}$ of 18.5 m/d at 295 K (71 degrees F), estimates can be made for other temperatures. These are provided in Table 1-2. A strong dependence on temperature is seen. At winter temperatures (around 0° C), the rate constant is about 8 times higher than at summer temperatures (around 20° C). This will have a large influence on calculated depositions in winter months.

Soldat (1963) also measured the concentration of ^{131}I on grass. When $K_{a/p}$ is calibrated to the grass data, a value of about 900 m/d is obtained. This leads to implausible results because the predicted concentration on vegetation would be higher than the total deposition over large areas would allow. For grass, alfalfa, or grain fields there is no bare soil, and the gas-to-plant transfer would be limited to the amount of ^{131}I available. This contradicts the initial assumption of constant air concentration, and so the original differential equation in this paper is not applicable for dense vegetation like grass or other cover crops.

1.4 Sagebrush Growth Model

The sagebrush life cycle has two growth peaks. The first peak is associated with leaf growth and occurs early in spring (February or March) when winter precipitation is available (the region is located in a winter-maximum precipitation regime). Most of these leaves drop at the first hot weather (about June). Sampling data on sagebrush leaf drop on a monthly basis are given by Rickard & Vaughan (1988) for two Washington locations. A second peak is associated with the reproductive stage in the fall (late September or early October); this phase lasts only a few weeks (personal communication, W. Rickard, July 1999). Total leaf

dry biomass ranges from a low of about 10 g/m^2 in the winter to 10-50 g/m^2 in the spring and fall peaks (Snyder et al. 1994).

Example randomized sagebrush biomass profiles in 1949 are provided in Figure 1-2. These biomass profiles are generated using a simple straight-line leaf growth and leaf drop model. Onset of the spring and fall growth periods are tied to the dates of the last spring frost and first fall frost obtained from historical records at 26 weather stations within the HEDR modeling domain. Data reported by Uresk, Gilbert, & Rickard (1977) indicate that the fall flowering period has a biomass about 60% the amount of the corresponding spring water-leaf dominated biomass.

1.5 Concentration Data from 1946

Beginning in late 1945, a substantial number of vegetation samples were collected regularly at standardized locations in the cities of Richland, Kennewick, Pasco, and Benton

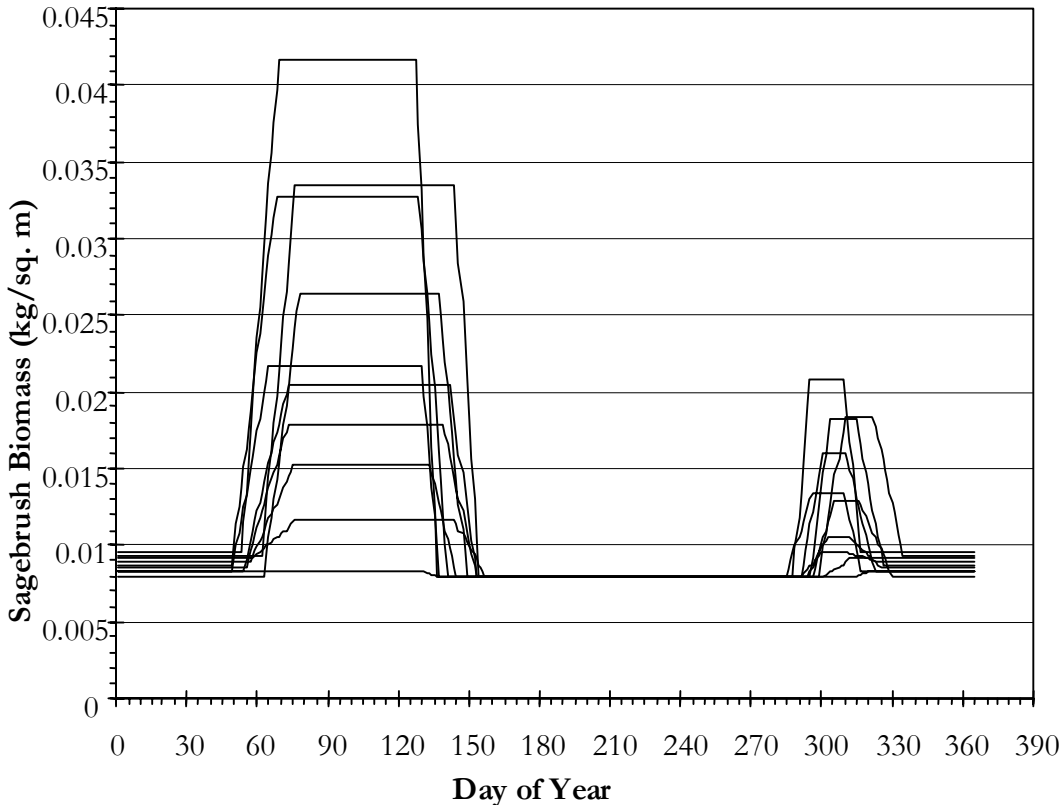

Figure 1-2. Example Replications of Sagebrush Biomass Profiles for North Richland Using 1949 Temperature Data.

City, Washington. Several locations within each city were routinely monitored. The most extensive data set for these locations was collected in 1946, the year of second-highest ^{131}I emissions (Heeb 1994; Heeb et al. 1996).

All transport, accumulation, and dose-related calculations have been performed on a spatial grid system. The grid consists of a rectangular set of nodes numbered sequentially, beginning in the southwest corner. The measurement sequences for Richland fall within two HEDR atmospheric dispersion nodes (469 for north Richland and 442 for south Richland); all of the measurements for Pasco and Kennewick fall within a single node (443); and the measurements for Benton City are on the edges of two nodes (467 to the north and 440 to the south). The northernmost of these Benton City nodes was selected for analysis as more representative.

Hanford historical monitoring data of ^{131}I in vegetation are available for the period beginning in mid-1945 through the present. The data for 1945-1947 are published by Denham, Dirkes, Hanf, Poston, Thiede, & Woodruff (1993). The data for 1948-1951 are published by Hanf, Duncan, & Thiede (1993). To account for biases that were historically not determined, HEDR staff developed conversion and correction factors. These are published by Mart, Denham, & Thiede (1993) for the 1945-1947 data and Denham, Mart & Thiede (1993) for the 1948-1951 data. Although the samples used to measure ^{131}I historically were most often labeled "vegetation," Denham, Dirkes, Hanf, Poston, Thiede, & Woodruff (1993) note that the samples were usually sagebrush.

These vegetation data are essentially all that are available from mid-1945 through 1950, the time period of high interest for atmospheric releases. The data are uneven in geographic coverage (most monitored locations are either on or close to the Hanford Site) and over time (the monitoring, with a few notable exceptions, was not routinely performed at repeated locations). There are over 3,500 samples reported for the year 1946. Of these, Richland has a complete history consisting of a total of about 550 values; Pasco and Kennewick, combined, have a total of about 645; and Benton City has about 200 values. Another 175 or so were taken at various points along a road west of Richland.

Because many of the data points appear to be reported in more than one source, there are significantly fewer values actually available than the 3,500 reported. Denham et al. (1993) provide original information in the form of laboratory counting records where

possible. However, in some instances, secondary references such as internal Hanford monthly or quarterly reports had to be used.

A third source of indeterminable authorship and quality is also available. Early in the HEDR Project, a hand-written compilation of data from the mid-1940s was found. This compilation is referred to as the "vegetation correlation data sheets," and evidently was prepared in the late 1940s or early 1950s. The data reported in it obviously duplicate much of what was found in the original counting laboratory records (dates and locations), and it also incorporates many of the later correction factors used to convert from counting data to concentration data (Mart et al. 1993). Because project staff have not been able to track the source of these data, they have not been accorded high reliability. However, this source does contain some data on ^{131}I concentrations in vegetation during the latter half of 1946 that is not available from other sources.

In 1946, contamination was measured with a Geiger-Muller detector directly on the vegetation samples (Mart, Denham, & Thiede, 1993). Gilbert, Mart, Strenge, & Miley (1992, p. 4.3) and Gilbert et al . (1996) indicate that the uncertainty in the conversion of these count data to concentration could be a factor of up to four for this period. Only the deterministic "best estimate" of Mart, Denham, & Thiede (1993, p. 7.2) has been used in these analyses. Incorporation of this uncertainty in the analyses would indicate a greater overlap than is apparent in the following figures.

1.6 Model Results for 1946

The new sagebrush growth and concentration models were incorporated in the DESCARTES computer code (Shipler et al. 1996; Miley, Eslinger, Nichols, Lessor, & Ouderkirk, 1994). Model results for the year 1946, based on 100 replications, are presented in Figure 1-3 for South Richland, Figure 1-4 for Pasco-Kennewick, and Figure 1-5 for Benton City. The figures show three curves as well as three types of sampled data. The three curves are the minimum, median, and maximum concentrations at each day of the year calculated from a suite of 100 replications. The modeled runs actually start on November 1, 1945, in order to account for the environmental accumulation from releases prior to January 1, 1946.

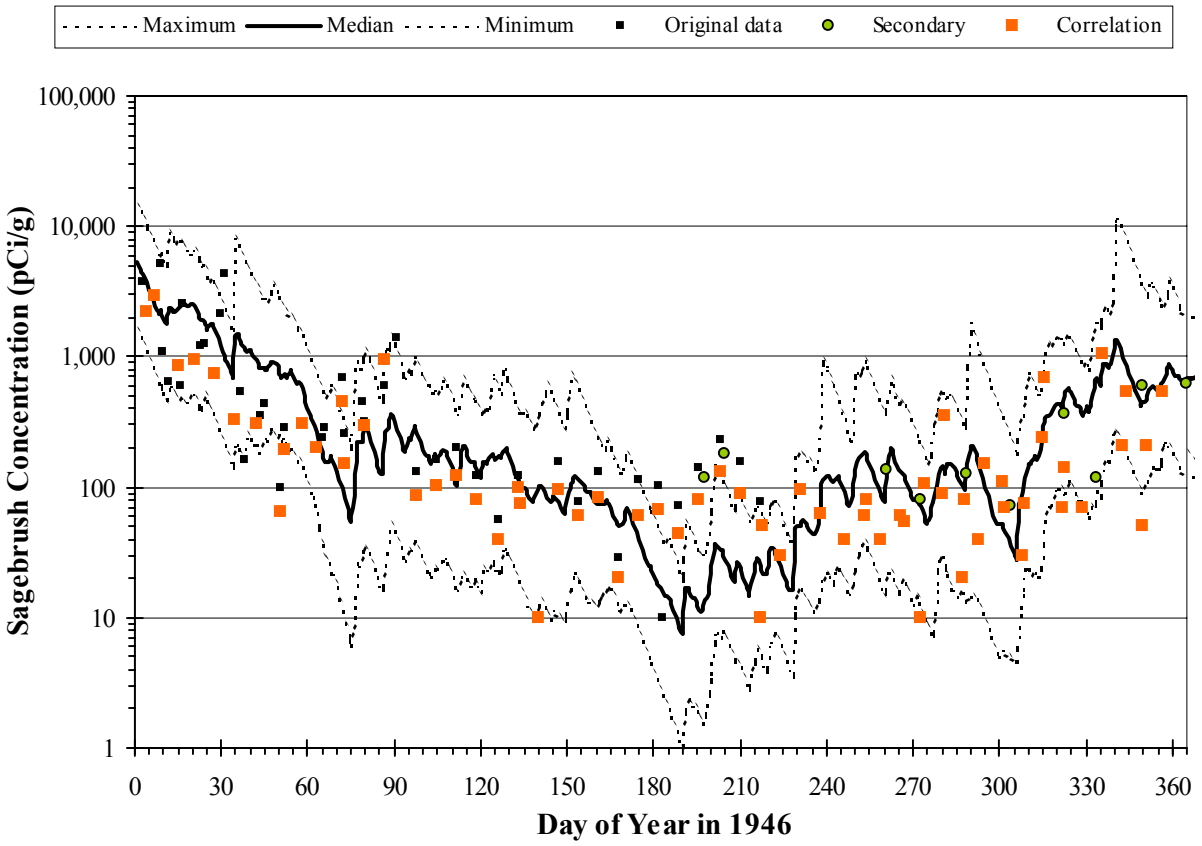

Figure 1-3. Comparison of sagebrush concentration projections with historical data in 1946 for North Richland (model node 442).

The revised model yields sagebrush concentrations that track the general shape of the sampled data throughout the year. The previous sagebrush model underpredicted sagebrush concentrations in winter by an order of magnitude or more (Napier et al., 1994). The comparison at Benton City is remarkably good, especially considering that Rattlesnake Mountain [elevation 1,050 m (3,445 ft)] lies between the major source of emissions [elevation about 223 m (730 ft)] and Benton City [elevation 150 m (490 ft)]. The atmospheric transport model in the RATCHET code (Ramsdell et al. 1996; Ramsdell, Simonen & Burk, 1994) used a wind field extrapolated from surface wind data. This validation result supports the use of surface wind data for the dose modeling studies. A scatter plot of historical sampled values against median modeled values for South Richland is provided in Figure 1-6. The scatter plot shows variability, but no significant bias towards underprediction or overprediction for any of the three major sources of historical data.

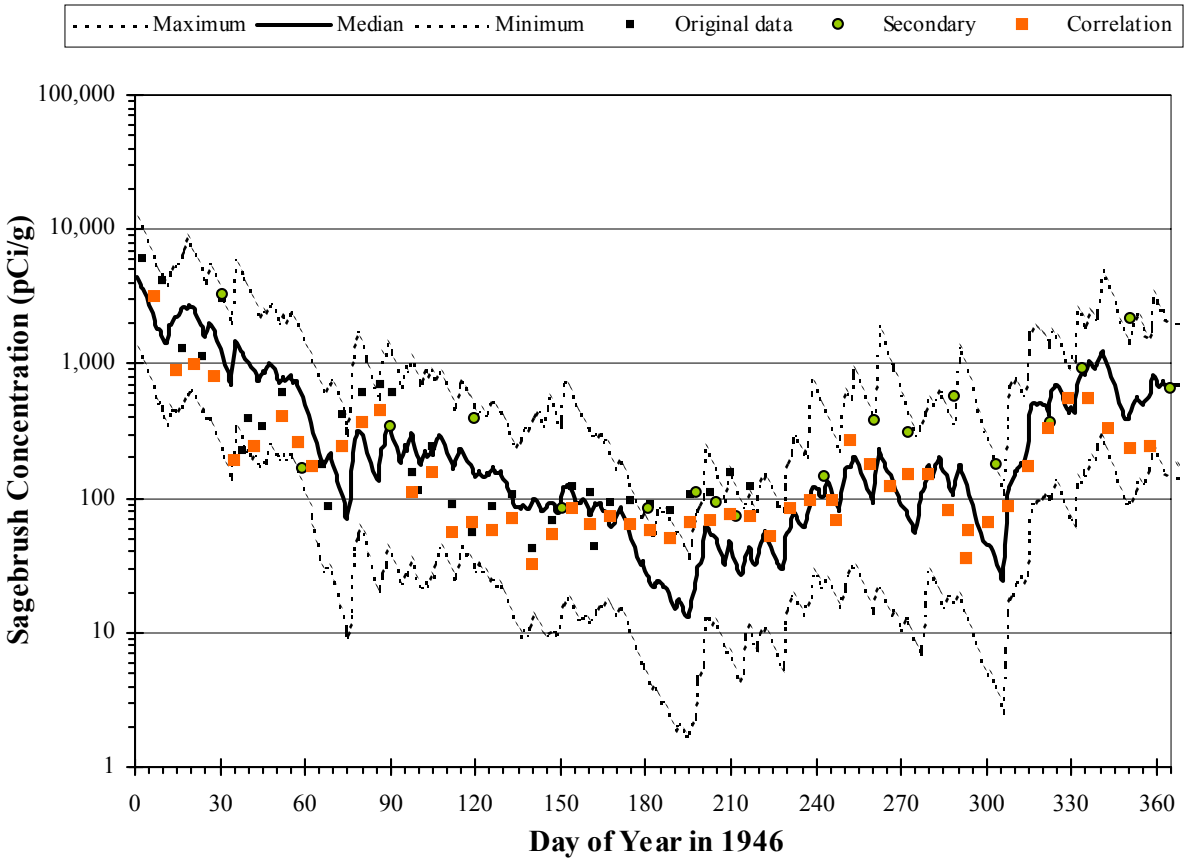

Figure 1-4. Comparison of sagebrush concentration projections with historical data in 1946 for Pasco/Kennewick (model node 443).

1.7 1949 Green Run Data

The Green Run experiment that began on December 2, 1949, was part of the development of monitoring methods for intelligence efforts directed towards the emerging Soviet nuclear program. A description of the experiment was prepared by Jenne & Healy (1950). In brief, a planned release of about 330 TBq (9,000 Ci) of ^{131}I to the atmosphere was made over a short period beginning late December 2, 1949. Extensive environmental monitoring efforts were made throughout the inland Northwest in the weeks following the release.

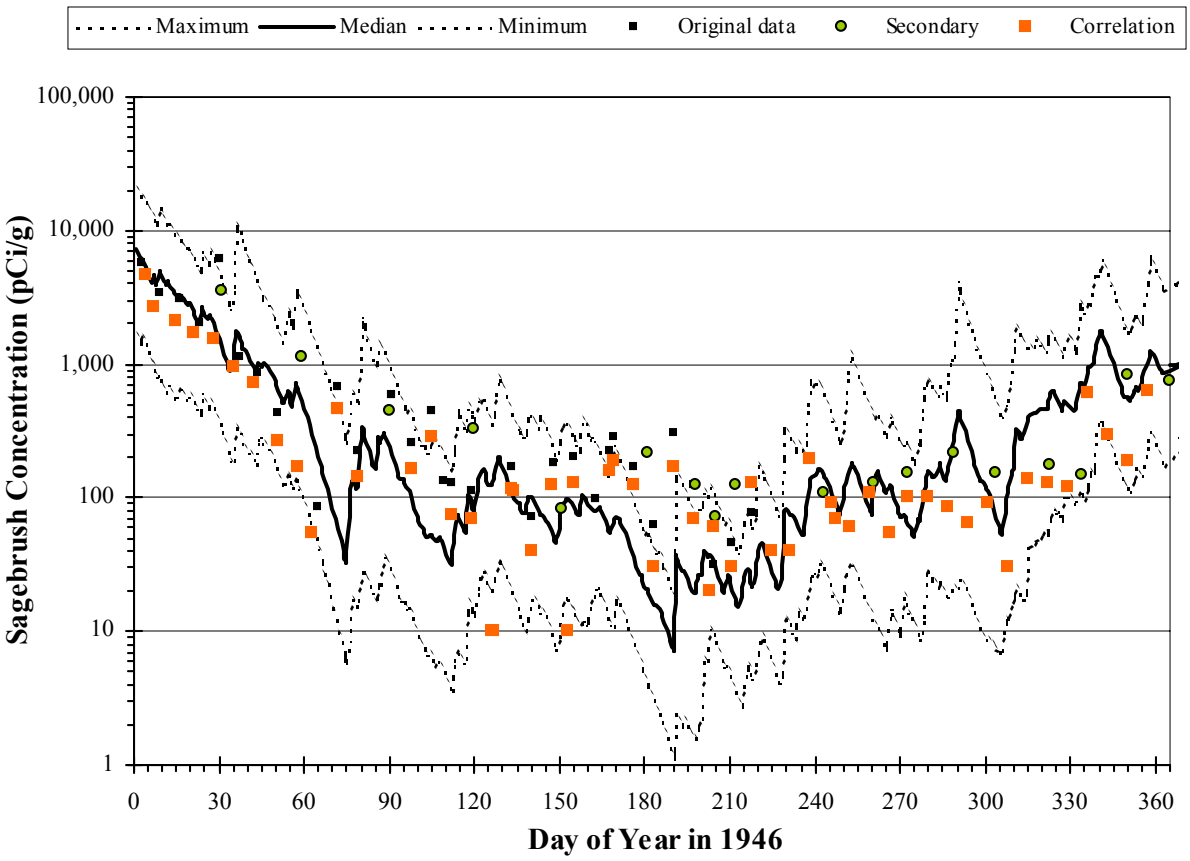

Figure 1-5. Comparison of sagebrush concentration projections with historical data in 1946 for Benton City (model node 467).

Sampling efforts intensified during and after the Green Run release. About 618 samples taken during the month of December 1949 are available throughout the HEDR atmospheric dispersion domain. Singlevich (1950) and Parker (1950) both report that 1,365 vegetation samples were taken. Many of these, however, were on the Hanford Site.

During the initial days after the release, most monitoring efforts concentrated on the Hanford Site. The first off-site forays were made on December 5. Two cars were sent north, one to Ritzville, Moses Lake, and Coulee City, Washington; the other to Walla Walla, Colfax, and Spokane, Washington. On December 6, these two groups continued east to Ellensburg and north of Spokane, Washington, respectively. Additional measurements were taken on December 7 between Yakima, Pasco, and Ritzville, Washington. Additional sampling was conducted on later days, but later dates were not modeled for this paper.

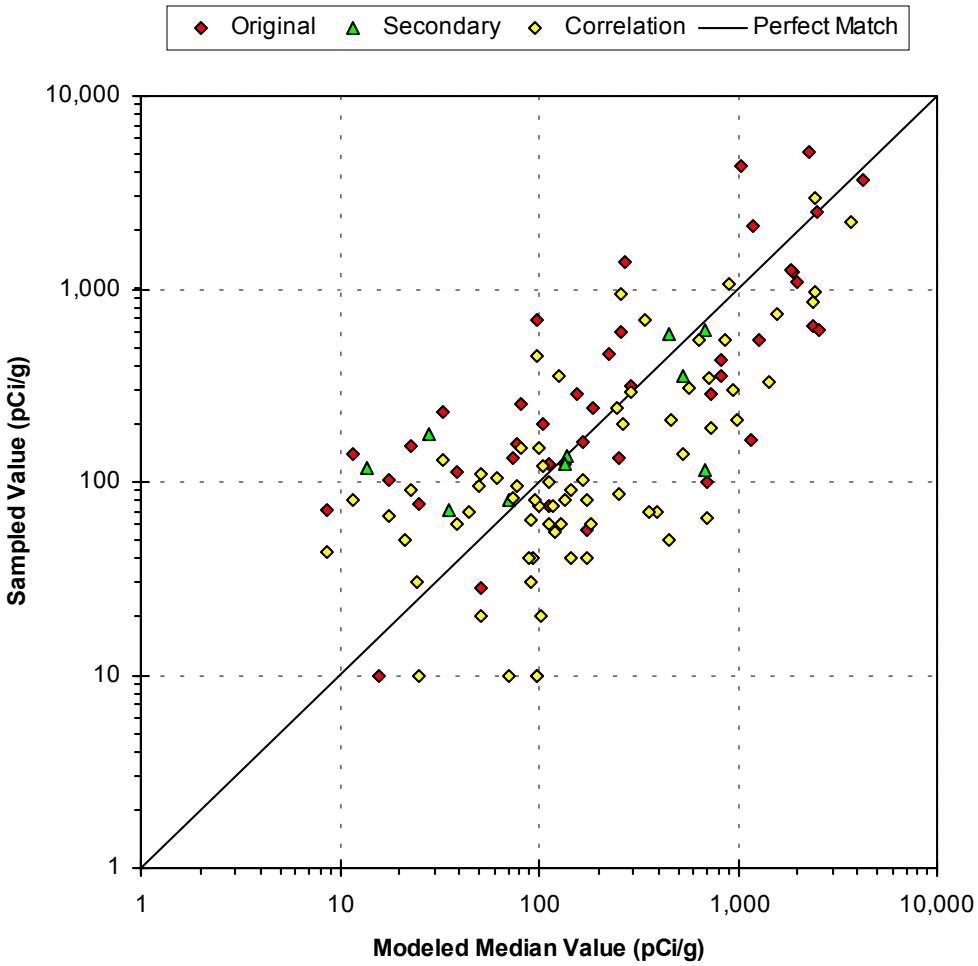

Figure 1-6. Scatter Plot of Historical Sampled Values Against Median Modeled Values for South Richland (model node 442).

By 1949, techniques for radionuclide detection in environmental samples had improved over those available in 1946. Concentration measurements of iodine-131 in vegetation were made with a multi-step chemical extraction process, in which the iodine-131 was removed from the sample and the resulting solution counted. This provided much better counting geometry and reduced the uncertainty about absorption of beta emissions within the sample. The conversion from detected counts per minute to concentration was made as described in Denham et al. (1993, p. 8.1). A complete description of the available information is provided in Hanf et al. (1993). Unfortunately, the laboratory used for counting the environmental samples was itself contaminated with ^{131}I during the course of the Green Run event, resulting in a detection limit of around 0.4 Bq/g (10 pCi/g) (Jenne & Healy 1950, p. 17).

1.8 Green Run Model Results

The 1949 green run data provide a look at the spatial validity of the model, whereas the 1946 data provided a look at the temporal validity at a few locations. Results for December 5 and 6, 1949, are provided in Figures 1-7 and 1-8, respectively. The contours on the plots are the median DESCARTES-modeled concentrations (from a suite of 100 replications) of ^{131}I in sagebrush. Each sampled data point is given a score in the range 1 to 6. The scores are defined as given in Table 1-3.

The historical meteorological information indicates that the wind velocity was rather slow and towards the southeast during the early period during and after the release. The plume would have drifted from the central Hanford site towards the city of Walla Walla, Washington, and stagnated in that area. The night of December 4-5, a cold front moved through the region from south to north, pushing the plume rapidly to the north.

Visual inspection of the results for December 5 and 6 (Figures 1-7 and 1-8) indicates that the primary plume had already passed by the time the monitoring crews arrived. The general footprint shape is influenced by the preceding three days' weather, moving first to the east and then the north. The plume footprint is decreasing in area over time through the decay of the ^{131}I. The scores on the figures indicate that the model is overpredicting the deposition on the southern and eastern sides of the footprint but doing well on the west. The deposition gradient is quite steep on the southeastern side of the footprint, and more gradual to the north and west in the direction the plume traveled.

If the model had a relatively small error in position as a function of time, a very minor misprediction from December 2 through 5 could be amplified. This possibility was investigated as a sensitivity analysis by shifting the pattern to see whether this would compensate for the general pattern of misprediction. If the calculated plume footprint is moved one or two calculational nodes to the northwest, the scores associated with each data point are greatly improved; nearly all fall into the range between 2 and 5. Apparently, the model predicts that, during the approximately 52 hours following the start of the release, the plume drifted about 15 km (10 mi) more to the southeast than actually occurred between December 2 and 4 (prior to the passage of the cold front). This misprediction of less than 0.3 km/hr (0.2 mph) is readily explained because of the integer nature of the historically available wind speeds.

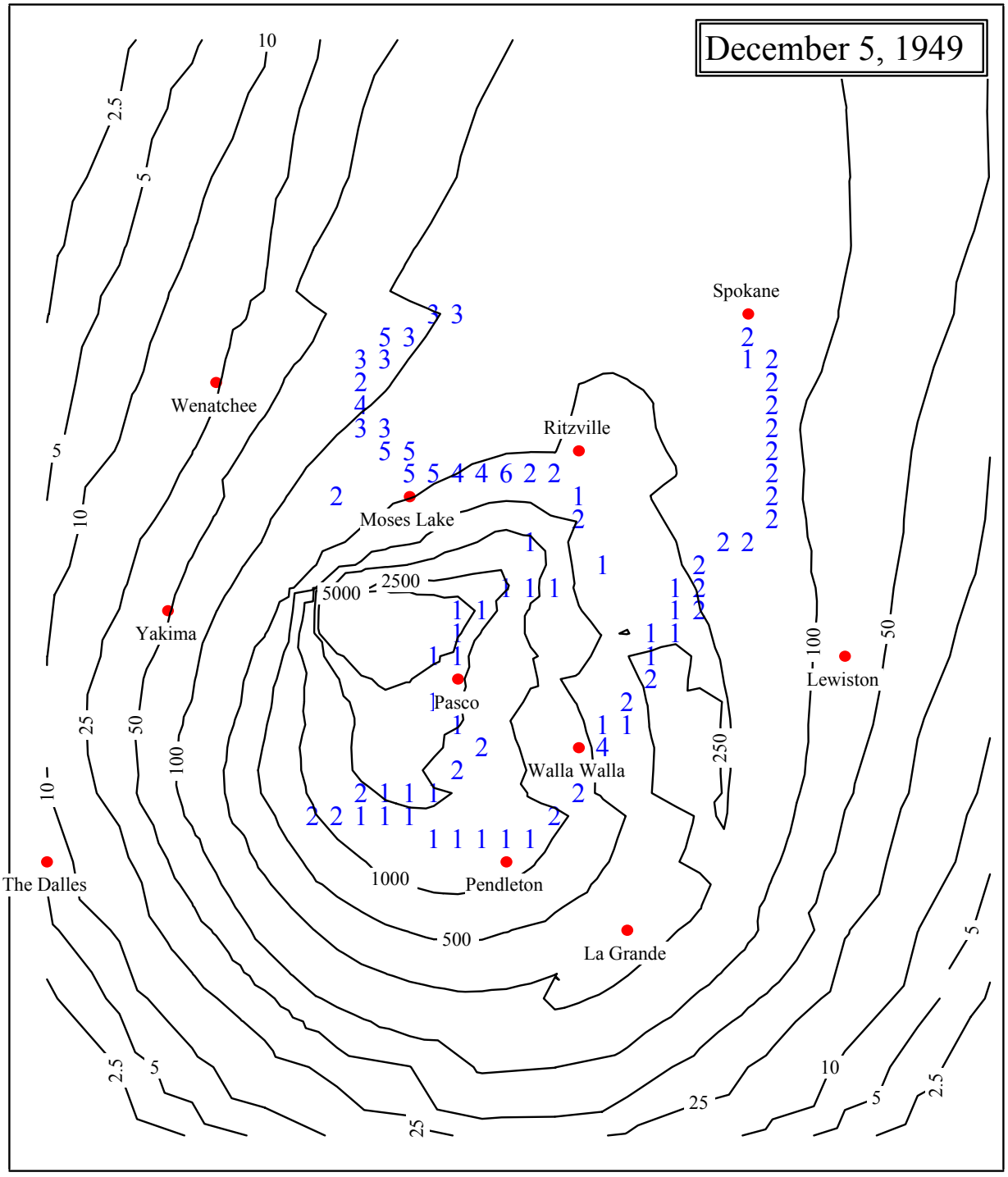

Figure 1-7. Map Illustrating Estimated Median Deposition of ^{131}I on Sagebrush for December 5, 1949, and Scores of Measured Data Relative to Estimated Concentrations.

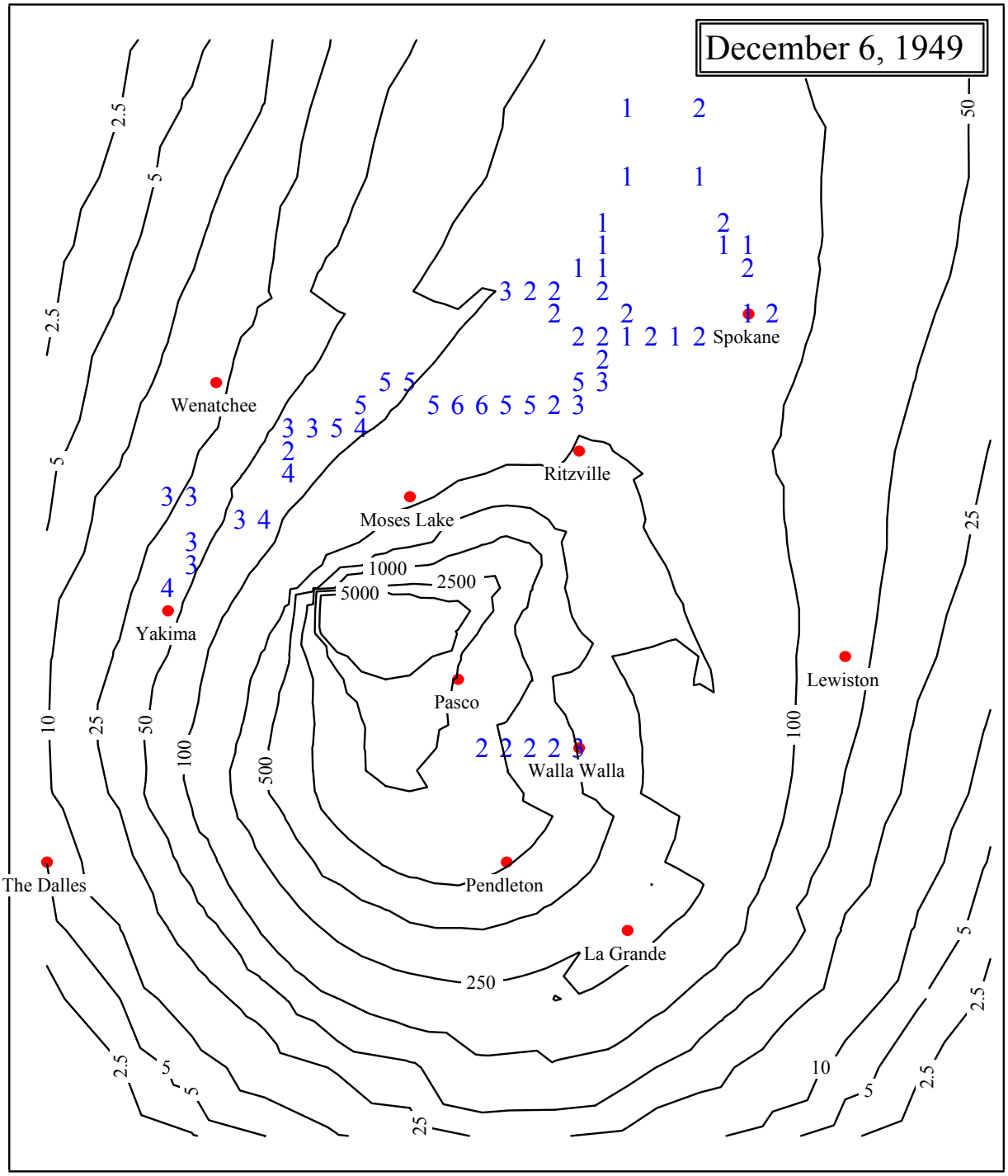

Figure 1-8. Map Illustrating Estimated Median Deposition of ^{131}I on Sagebrush for December 6, 1949, and Scores of Measured Data Relative to Estimated Concentrations.

Table 1-3. Explanation of the Sample Scores for Figures 1-7 and 1-8

Score	Explanation
1	The sampled value was below the smallest modeled value
2	The sampled value was between the minimum and 25th percentile of modeled values
3	The sampled value was between the 25th percentile and the median of modeled values
4	The sampled value was between the median and 75th percentile of modeled values
5	The sampled value was between the 75th percentile and maximum of modeled values
6	The sampled value was above the largest modeled value

1.9 Model Validation Summary and Conclusions

A temperature-driven model for ^{131}I on sagebrush has been implemented in the HEDR environmental accumulation model. This model includes a realistic biomass growth model for sagebrush and a thermodynamic model of air-plant deposition.

This model is specific to sagebrush in the regions of eastern Washington State. The results for summer months are similar to those obtained using the traditional deposition/interception model, but the temperature-dependent model for ^{131}I accumulation on sagebrush presented here provides a good fit to the historical data for releases from the Hanford site over the entire annual temperature cycle. It is a significant improvement over the air-interception fraction models used in earlier studies. The temperature dependence is required to match historical data from cold weather months.

These results validate the ^{131}I source term, atmospheric transport, and environmental accumulation models used by the HEDR project for these time periods. The time-series results for Richland, Kennewick-Pasco, and Benton City indicate that the models have an excellent ability to track the measured concentrations over time at specific locations. The Benton City result is particularly striking, because this location is shielded from the source by a 1,050-m (3,445-ft) mountain. For the 1949 single release, the models predicted the appropriate shape and magnitude of the resulting deposition footprint, but slightly mispredicted the location (by about 15 km within a 200,000 km^2 calculational domain). The model predictions were very close to the actual occurrence for this single event. On a long-

term average over a large number of releases (the design intent of the models), the effects of exact locations of individual plumes should tend to average out.

1.10 References for Section 1

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2. Estimation of wind fields for the RATCHET code

The National Academy of Sciences review of the HTDS dosimetry noted that the RATCHET model has a significant source of uncertainty built in: the interpolation of the wind fields from historically monitored wind speeds and directions at regional weather stations. The NAS suggests that "there should at least be a study of the sensitivity of the dispersion estimates with respect to local errors in the wind field. According to Ramsdell et al. (1994), inverse-square-distance weighting was used for interpolation. That method does not produce any information about the uncertainties associated with the interpolated values. The paper does not justify the choice of a method; in particular, it is known to be very sensitive to the location pattern of the data points. Inverse-square-distance weighting is known to be "isotropic"; that is, it incorporates the distance from the data points to the interpolation point but not the directions. In the case of wind fields, one would expect the direction from an interpolation point to a data point to be important. The algorithm is also insensitive to the directions between the pairs of data points; it incorporates only their relative distances from the interpolation point."

It is apparent that the NAS reviewers did not have access to a directly relevant report. The HEDR project report by J.V. Ramsdell and E.D. Skyllingstad entitled *A Review of Wind Field Models for Atmospheric Transport*, PNWD-2148 HEDR (1993), addresses most of these concerns directly. A copy of this report has been provided to the HTDS staff. A summary of the report and its pertinent points follows. Other reports that also address this issue include Ramsdell (1992) *Summary of the March 25-26, 1991 Atmospheric Model Working Meeting*, and Nappo (1992) *Review of the Regional Atmospheric Transport Code for Hanford Emission Tracking (RATCHET)* .

The report *A Review of Wind Field Models for Atmospheric Transport*, PNWD-2148 HEDR (1993), was produced by the technical task that estimated the transport and deposition of radionuclides released to the atmosphere. The report describes methods used to transform observed wind data into wind fields. The wind fields are prepared in the Regional Atmospheric Transport Code for Hanford Emission Tracking (RATCHET) and used to determine where the radionuclides went after being released to the atmosphere. Wind fields play an essential role of the process of estimating the air concentrations and surface contamination at specific locations in the vicinity of Hanford.

This report describes the procedure used in the transformation of observed wind directions and speeds to wind fields for use in atmospheric transport calculations in RATCHET. The report discusses alternative procedures described in the literature and evaluates the alternatives based on the

wind data available for use in the HEDR Project. Wind data from 1944 to 1950 for the region around the Hanford Site are described in a separate report by Stage et al.

Techniques for preparing wind fields are evaluated on the basis of their data needs. Not all techniques for wind field estimation are appropriate for the HEDR Project because of the limited data available for the study.

This report focuses on RATCHET. Specifically, it describes procedures for estimating wind fields from observed (measured) wind data. Wind fields are used to calculate the transport of radionuclides released to the air from Hanford operations. Figure 2-1 shows the process that occurs within RATCHET. Observed wind data are used to generate wind fields. These fields are then used to move the puffs containing radionuclides within the model domain. Ultimately, the radionuclide concentrations in puffs are used to calculate time-integrated air concentrations and surface contamination at specific locations. Thus, wind fields are key elements in the process of estimating air concentrations and surface contamination at specific locations.

2.1 Model Domain And Wind Data

The intended use of the RATCHET code is to calculate daily time-integrated air concentrations and surface contamination in eastern Washington, northeastern Oregon, and northern Idaho for the period from December 1944 through 1949. The atmospheric model domain (shown in Figure 2-2) covers about 75,000 sq. mi. It is a rectangle centered at 46° 40' N, 118° 45' W. The Hanford Site, shown by the hatched area, is slightly west of the center of the domain. Distances within the domain can be determined using the tick marks on the domain border, which are spaced at 12-mi intervals.

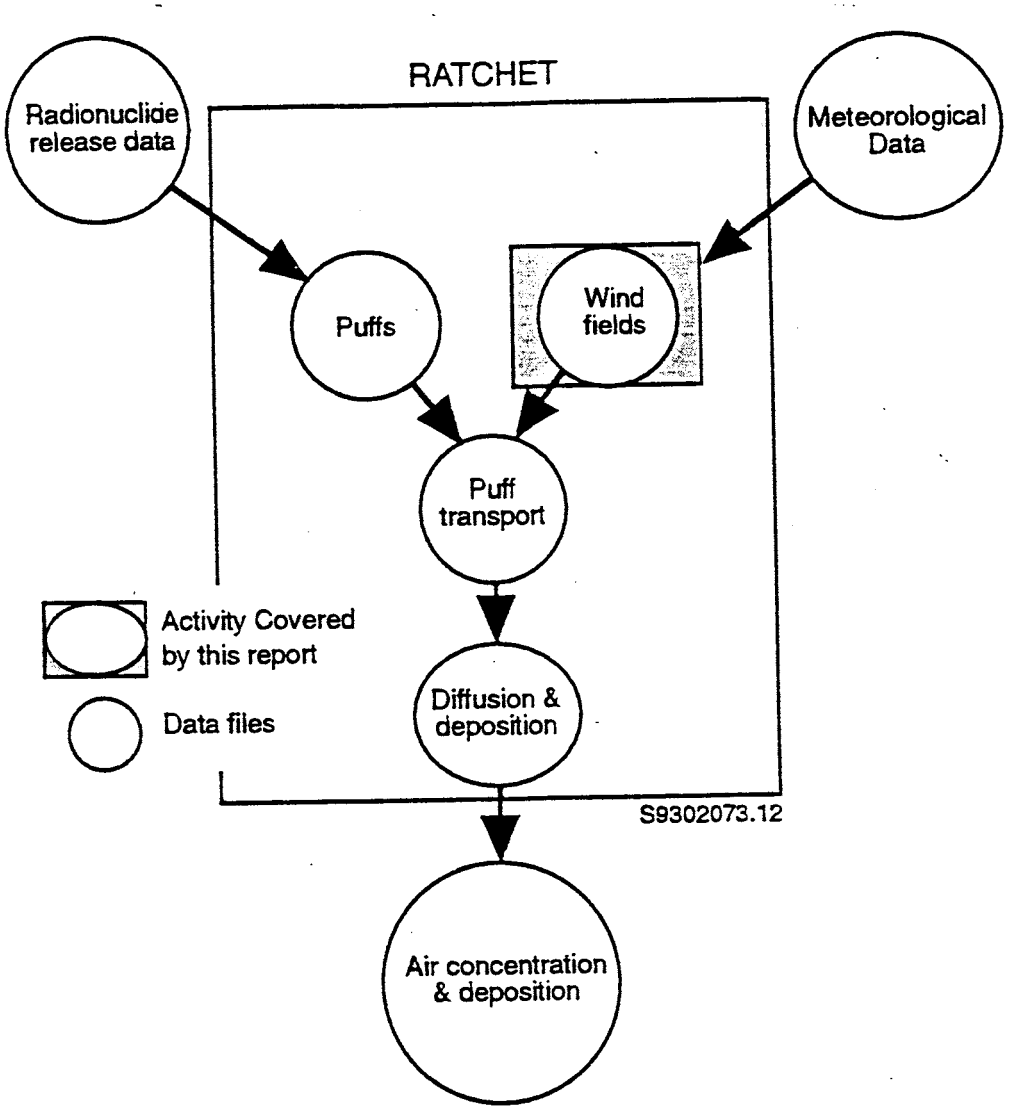

Figure 2-1. RATCHET Procedure to Prepare Wind Fields/Move Puffs

There are meteorological data for 25 locations in and adjacent to the atmospheric model domain. Figure 2-2 shows these locations. However, data are not available for all of the locations for the full period under consideration. Typically, at any time, available meteorological data are limited to 10 to 15 locations. The meteorological records available for the HEDR study period are described by Stage et al. (1993). The records contain data from surface meteorological observations the domain. Distances within the domain can be determined using the tick marks on the domain border, which are spaced at 12-mi intervals.

Atmospheric dispersion models frequently use upper-air wind and temperature data obtained with balloon-borne instruments. Unfortunately, no upper-air data are available for the mid-1940s

for the HEDR atmospheric model domain. The first measurements of this type were not made until the late 1940s, well after the period of the maximum releases to the atmosphere. As a result, the atmospheric transport and dispersion estimates for the HEDR Project must be based on surface meteorological data.

From 1944 through 1949, meteorological observations were made and recorded at hourly intervals on the half hour. Wind speed observations were made by an observer watching a dial for a 1-min period and recording an estimate of the average speed, in knots. Wind direction observations were made by watching lights on a compass dial and recording the direction in compass points (22.5° wide sectors). Hanford wind records are an exception to the general rule. Hourly-average wind directions and speeds were estimated from data recorded on strip charts. Wind speeds were recorded in miles per hour, and wind directions were recorded to the nearest 10°.

Figure 2-2 provides an indication of the general topography in the area. The figure shows the relatively flat mid-Columbia River Basin and the mountainous regions that surround the basin. It can be seen that many of the meteorological stations are in places where topography could have had an influence on the observed winds. Stage et al., (1993) discuss the potential topographic effects at each location.

2.2 Wind Field Estimation

The RATCHET computer code implements a puff diffusion model. A series of circular puffs is used to represent the plume that contains the material released to the atmosphere. Each puff is characterized by the position of its center, horizontal and vertical diffusion coefficients, and the amount of material in the puff. The wind at the center of each puff is used to calculate the puff's movement. These winds are allowed to change as a function of time and space. Therefore, the code must include a procedure for estimating the wind at the positions of puffs from available wind data.

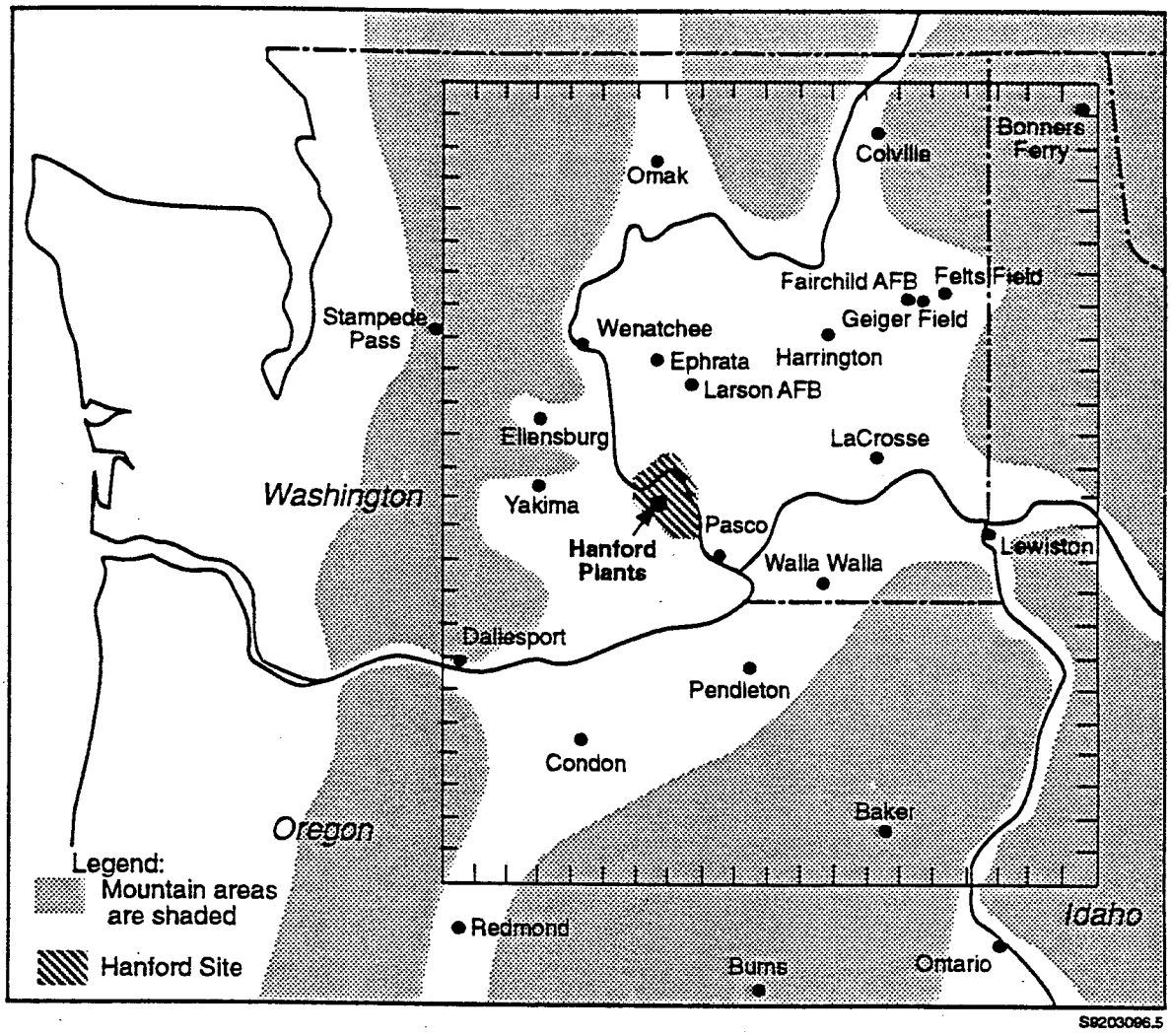

Figure 2-2. Meteorological Stations within the HEDR Atmospheric Domain

Wind data are used to define wind fields, and the winds at puff positions are calculated from the wind fields. The wind field in RATCHET represents winds at 10 m above the ground. Surface wind measurements were not made at this height in the 1940s. Therefore, the observed wind data are adjusted to a height of 10 m prior to preparation of the wind field. Similarly, puffs are released at heights above 10 m, and the winds at the release height are estimated from winds at 10 m. A wind profile model is used in both cases.

In RATCHET, the wind field is defined at equally spaced nodes within the atmospheric model domain. This type of wind field representation is called a gridded wind field. If upper-air wind data were available, gridded wind fields could include specification of the wind at several levels

in the vertical at each node. After the gridded wind field is calculated, the winds at puff positions are determined by interpolation as needed.

This report is primarily concerned with the preparation of gridded wind fields. Preparation of gridded wind fields has three steps. The first step involves adjustment of the measured winds to a standard reference height. The second step uses a combination of interpolation and extrapolation to make an initial estimate of the field. Throughout the remainder of this report, the term interpolation will implicitly include extrapolation, if appropriate. The third step involves adjustment of the initial gridded wind field to make the field conform to some predefined criteria. One common set of criteria limits the implicit vertical component of the wind vector and adjusts the horizontal components to conserve the mass of the air. Many atmospheric diffusion models skip this third step.

Interpolation of wind data to the nodes of the grid is usually done using one of several weighted averaging techniques. In these techniques, weights are assigned to the individual wind observations as a function of distance between the grid node and the observation point. The choice of weighting techniques is generally a subjective decision made by the modeler. Many factors, including the number of measurement locations and the topography surrounding the stations, may be considered in selecting a weighting technique.

After an initial estimate of the wind field has been made, the wind field may be adjusted to conform to criteria established by the modeler. Frequently, adjustment techniques are used to produce what are commonly referred to as mass-consistent wind fields. These techniques compute a vertical motion field from the original two-dimensional, horizontal wind field, constrain the vertical motions, and adjust the horizontal winds to conserve air mass. The adjustment techniques used to produce mass-consistent wind fields require information about the atmospheric structure (such as the upper-level winds, stability, and mixed-layer height) and use more sophisticated mathematics than basic interpolation methods.

The most advanced adjustment techniques involve the use of numerical models to predict changes in the winds. With these methods, gridded wind fields and temperatures are used to initialize a numerical model. Then, the model is used to simulate winds until the next observation period. In this way, the winds can be made to satisfy the full set of equations of motion. However, the computational requirements of these models limit their operational use and exceed the resources of the HEDR Project

2.3 Model Uncertainty

The HEDR codes, including RATCHET, are designed to account for uncertainty in input data. This is accomplished using Monte Carlo techniques. The full set of HEDR codes is executed a number of times using different input and parameter values. Selection of the input and parameter values for each run is subject to the constraint that all values must be consistent with available data. The results of each run represent one estimate of what might have actually occurred. Uncertainty is represented by the differences in results among the runs.

This section of the report describes the uncertainties in the input data available for use with the RATCHET code. The uncertainties exist in meteorological data and in the atmospheric release source term. A qualitative understanding of the uncertainties associated with the imprecision of the meteorological data and the timing of atmospheric releases provides a basis for evaluation of the importance of other sources of uncertainty. The last part of the section presents preliminary results from 100 realizations of the RATCHET code for 1945 to provide an indication of the ranges of time-integrated air concentrations that result from incorporation of uncertainty in the model.

2.4 Wind Data Uncertainty

The RATCHET code treats one form of uncertainty in wind data explicitly. That form of uncertainty is imprecision in the recorded values. The wind data for each station consist of a wind direction sector and a wind speed, which is recorded as an integer. As the hourly data for each station are read by the code, a specific wind direction within the reported wind direction sector is randomly selected as an estimate of the actual average direction for the hour. Similarly, a wind speed is selected that is within the range of precision of the recorded value. For the Hanford Meteorological Station a wind direction is selected from a 10° sector, and a wind speed is selected within ±0.5 mph of the recorded speed. For other stations the width of wind sectors is 22.5°, and the precision of the wind speeds is ±0.5 kn. The random wind direction and speed components differ from station to station, hour to hour, and run to run.

There are two additional sources of uncertainty in wind data that are not accounted for in RATCHET that might be considered. The first of these in uncertainty associated with winds at low wind speeds, and the other is the uncertainty associated with using a 1-min observation to represent an hourly average.

For wind speeds near the threshold of the instruments, there is a large uncertainty in both the direction and speed. Schere and Coates (1992) assume that uncertainty in both wind speed and

direction are related to the reported wind speed. The uncertainty in speed varies from 2 m/s in calm conditions to 1 m/s at high speeds. For near calm conditions, the wind direction is randomly varied through 360°. As the wind speed increases, the random variability in wind directions decreases to a few degrees (<6° when the wind speed is 10 m/s).

The RATCHET code does not account for the uncertainty associated with using 1-minute observations to represent hourly-average winds. This uncertainty should be somewhat less than the changes in wind direction from one hour to the next. The wind direction differences for 1-hour time lag provide a qualitative indication of the magnitude of uncertainties that might be associated with use of 1-minute observations. The standard deviation of the differences in wind direction at the 200-foot level of the HMS tower for consecutive hours (lag = 1 hr) is about 40°. However, the HMS data are estimates of hourly-averages taken from strip charts. Therefore, larger uncertainty might be expected at the remaining stations. The standard deviations of differences in wind directions for consecutive hours at Walla Walla and Fairchild Air Force Base were computed from station data in the HEDR meteorological database. The standard deviations are 47° and 38°, respectively. Thus, we conclude that the use of the 1-minute observations should be of the order of 30° to 50°.

2.5 Hourly Release Rate Uncertainty

There is another source of uncertainty in the input to RATCHET that is equivalent to uncertainty in winds. That source of uncertainty is the uncertainty in the hourly release rates. Heeb (1992) discusses the preparation of hourly release rates. These release rates include uncertainty in the time that each release started, the duration of each release, and in the amount released. The uncertainty in the start of releases varies from a few hours to a day or two. In general, it is of the order of one shift (8 hours).

Wind direction data from the 200 ft level of the Hanford Meteorology Tower, and from Walla Walla and Fairchild Air Force Base have been examined to assess the relationship between uncertainty in release time and uncertainty in wind direction. Figure 2-3 shows the frequency distributions for the difference in wind directions at the 200-foot level of the HMS tower for observations separated by one, two, six, and twelve hours. In each case the distribution is approximately symmetrical with a maximum at zero. However, the width of the distribution increases as the time between observations (lag) increases. The standard deviation of the differences

for lags from 0 to 24 hours are shown in Figure 2-4. The standard deviation reaches a maximum for lags of about 12 hours. This maximum, along with the decrease in standard deviation for longer lags, is caused by diurnal wind patterns. Wind directions for 1945 through 1947 from Walla Walla and Fairchild Air Force Base near Spokane were also examined.

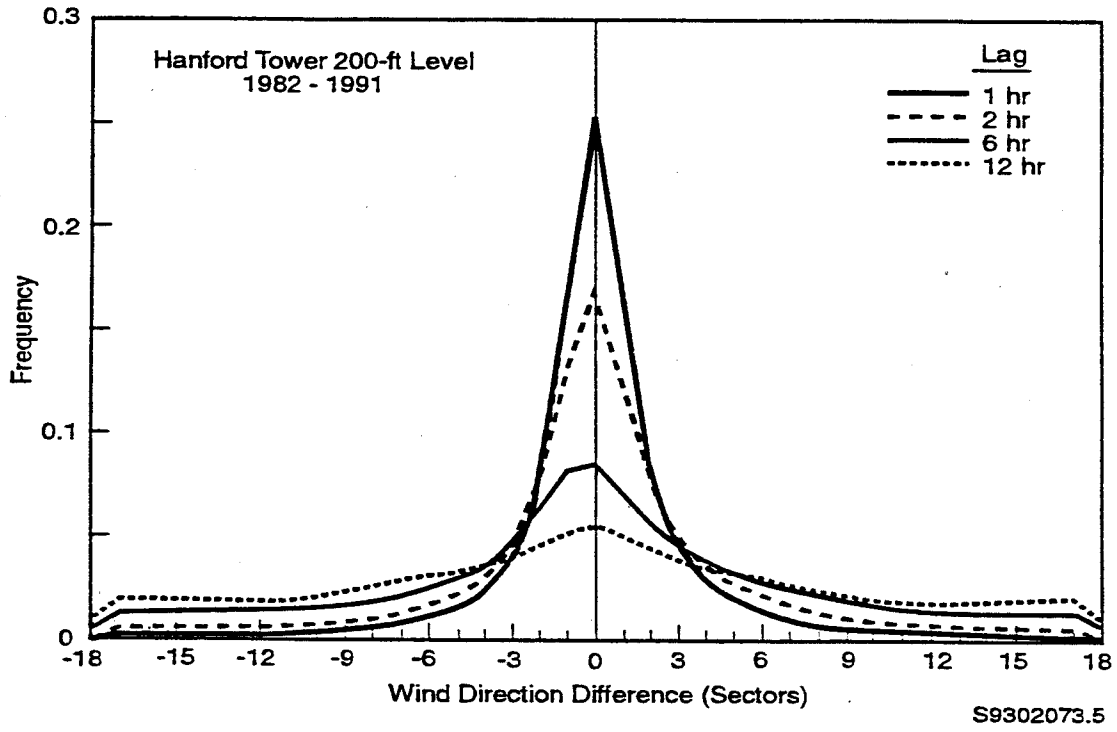

Figure 2-3. Frequency of Wind Direction Shifts at the HMS Tower

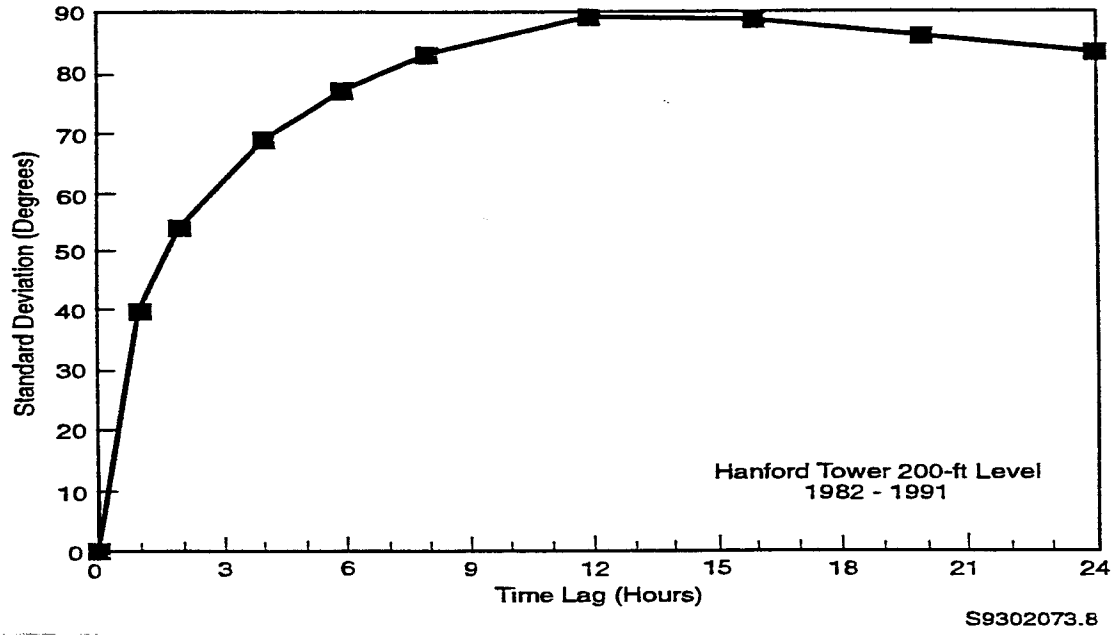

Figure 2-4. Standard Deviation of Wind Direction Differences as a Function of Time Lag

The frequencies that wind directions from observations made 8 hrs apart fall within a common sector have been determined from data from HMS, Walla Walla, and Fairchild AFB. Figure 2-5 shows how this frequency increases as the sector width increases. The sector width must be increased to about 90 degrees before there is a 50 percent likelihood the directions will be in the same sector. Again assuming that uncertainty in release times can be associated with lag times between observations, Figure 2-5 indicates the wind direction uncertainty associated with an 8-hour uncertainty in release times is 80 to 100 degrees.

A rough comparison can be made between the uncertainty in the use of 1-minute observations to represent hourly average winds and the uncertainty associated with release times. Figure 2-6 show the change frequencies of consecutive hourly wind direction observations falling in a common sector with change in sector width. Approximately 50 percent of the time, the wind directions in consecutive observations will be within a sector 30 degrees wide. If this width represents the uncertainty associated with 1-minute observations and the 90 degree sector width from Figure 5-5 represents the uncertainty associated with release times, the uncertainty in release times is much more significant than the uncertainty in the 1-minute observations.

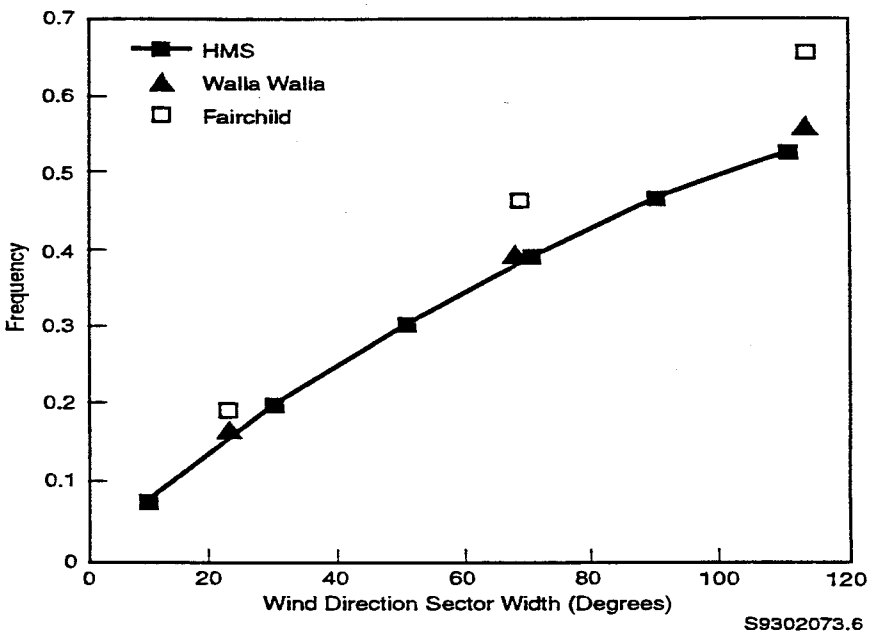

Figure 2-5. Cumulative Frequency of Wind Direction Differences for Observations Separated by Eight Hours (HMS, Walla Walla, and Fairchild AFB)

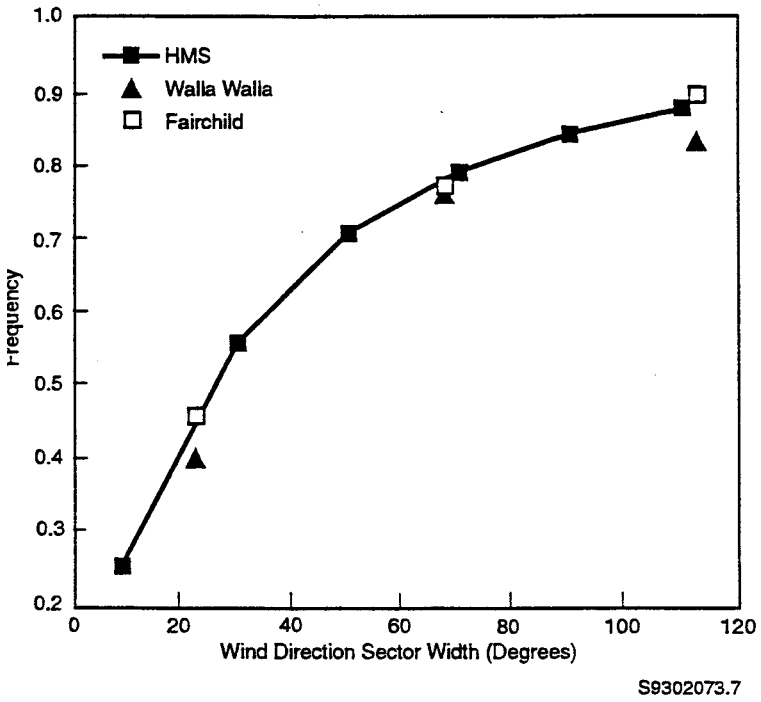

Figure 2-6. Frequency of Consecutive Wind Direction Observations in a Common Sector (HMS, Walla Walla, and Fairchild AFB)

2.6 Preliminary Estimates Of Model Output Variability

The uncertainties in wind direction associated with uncertainties in release times are large. These uncertainties are directly related to the initial transport direction. If the HEDR project were concerned with hourly dose estimates, the uncertainties in wind direction would lead to larger, and perhaps unacceptable, uncertainties in the dose estimates. However, the HEDR project is concerned with annual dose estimates. Therefore, it is appropriate to ask how the estimates of annual time-integrated air concentrations and surface contamination vary in uncertainties in response to uncertainty in model input.

The RATCHET code has generated 100 realizations of time-integrated air concentrations and surface contamination for use in model evaluation studies. Figure 2-7 shows the locations of 43 nodes within atmospheric model domain that have been given names. Figure 2-8 provides an indication of the geographical pattern of time-integrated air concentrations based on median values at the 43 named nodes. The pattern, although well defined, is somewhat broader than would be expected for an individual realization.

The pattern in Figure 2-8 is consistent with patterns found in previous studies of dispersion from Hanford (Hilst 1951; Nickola 1951, 1952, 1953). As a result, there is some assurance that there are no major errors in the processing of wind data in RATCHET. However, the figure does not indicate the range of variation of time-integrated air concentrations at each node within the 100 realizations. Table 2-1 lists the tenth, fiftieth, and ninetieth percentile time-integrated air concentrations for each of the nodes. At 28 of the 43 named nodes, the 90th percentile time-integrated air concentration was less than a factor of two larger than the 10th percentile value. And, at only one node (Meadows, Idaho) did the 90th percentile value exceed the 10th percentile value by more than a factor of 5. This node, in the extreme southeast corner of the model domain, also has the lowest median time-integrated concentration of the 43 named nodes.

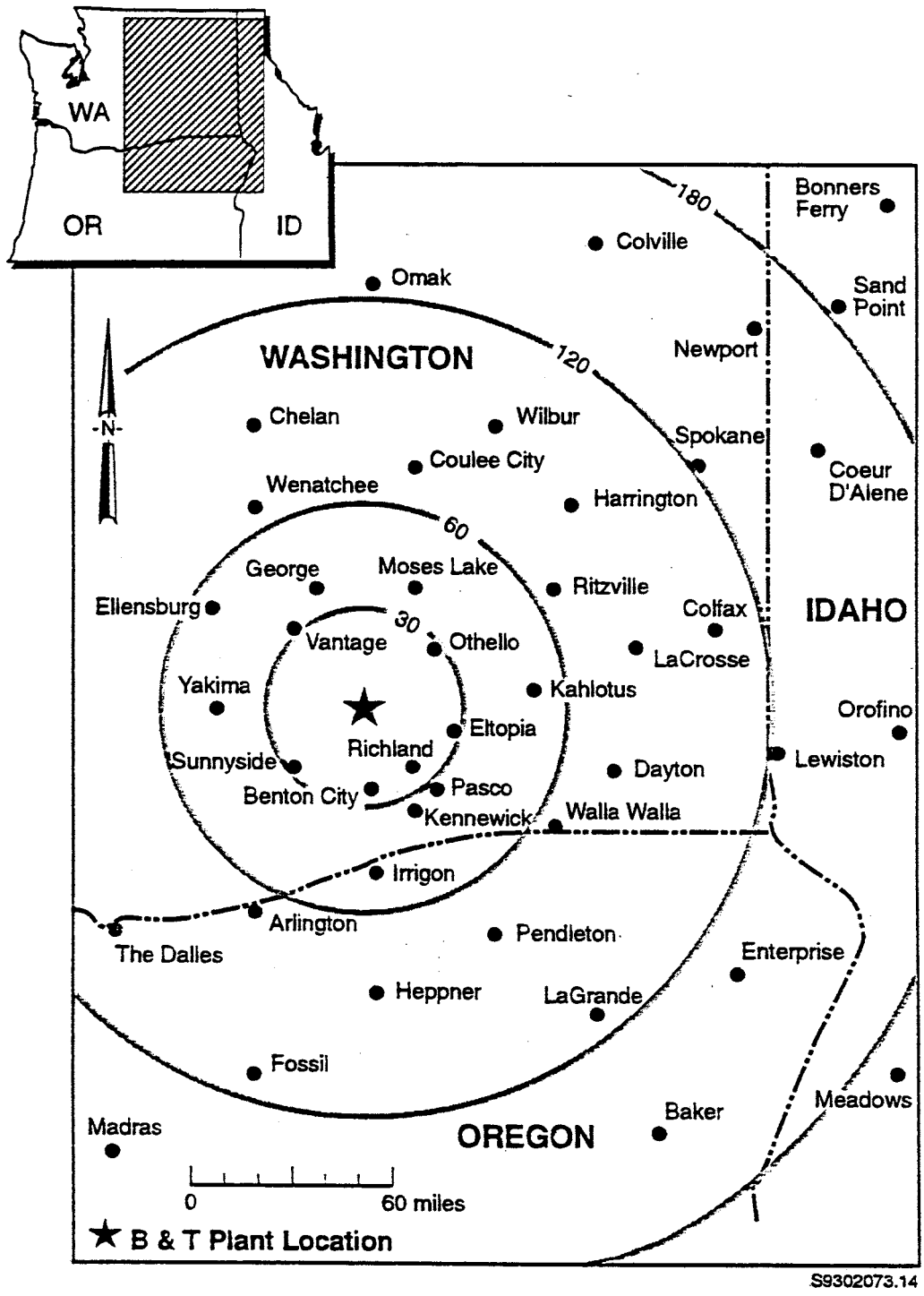

Figure 2-7. Named Node Locations within the HEDR Atmospheric Domain

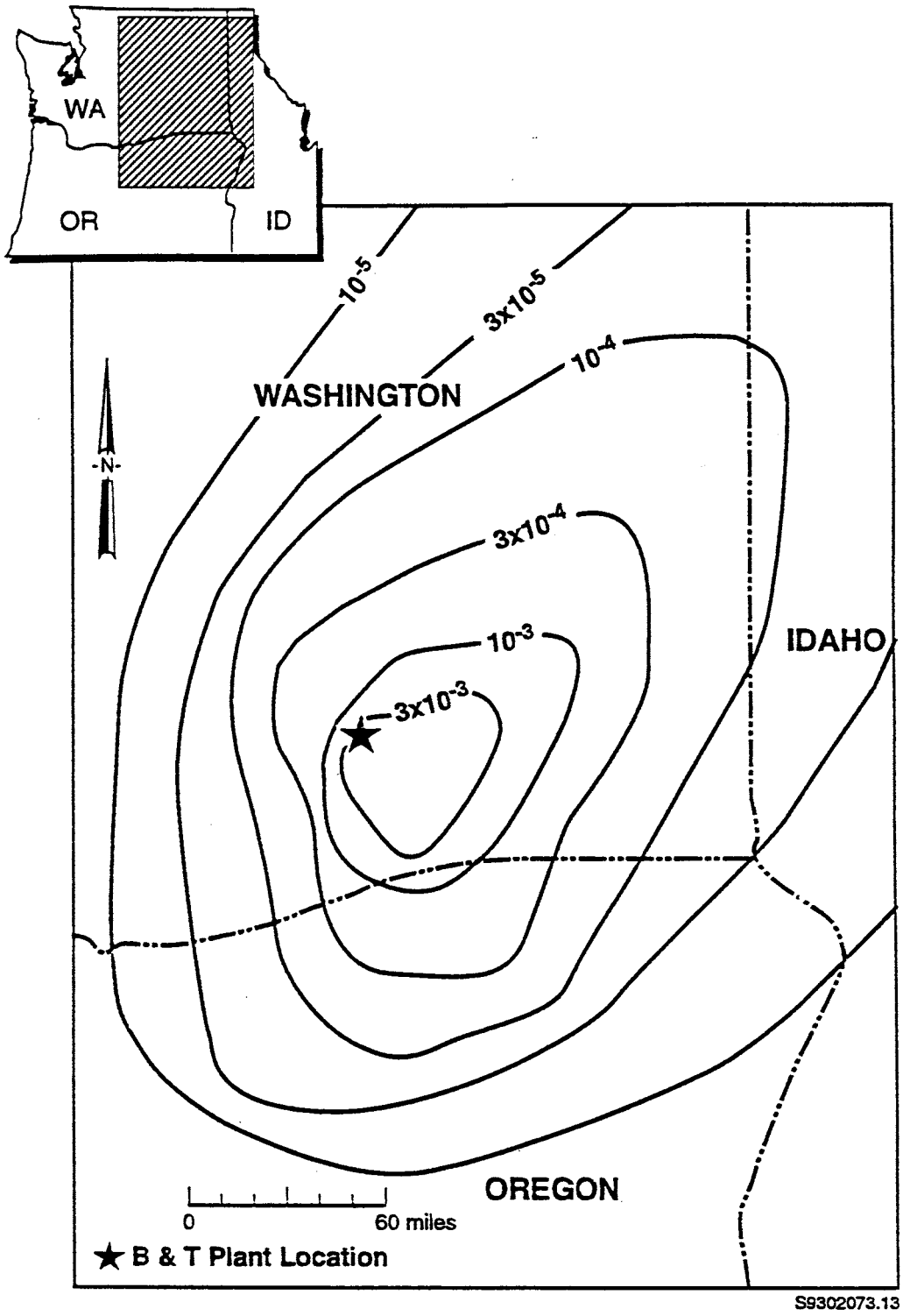

Figure 2-8. Geographical Pattern of Median Iodine-131 Time-Integrated Air Concentrations [(Ci-sec)/m^3] (1945)

It is clear from the values in Table 2-1 that rather large uncertainties in the hourly release rates and station winds do not result in large variations of annual time-integrated air concentrations between model realizations. The integration over time performed by the model filters out most of the variability in model input. This finding is consistent with the improvement in dispersion model performance as the time period being modeled increases that has been reported by model evaluation studies, e.g. Weber, et al. (1984); Carhart, et al., (1989); Klug, et al., (1992). It is reasonable to interpret this result as indicating that climatological patterns are more important for estimating dispersion of continuing long-term releases than individual hourly patterns.

2.7 Wind Field Models

There are several ways of representing the spatial variation of wind in atmospheric dispersion models. Wind fields may be specified using polynomial functions that permit direct calculation of winds at puff positions. However, most models, including RATCHET, use gridded wind fields to calculate the transport of material.

Observed wind data are rarely, if ever, available for the nodes on a grid covering the domain of atmospheric transport model. Therefore, the model must generate gridded wind fields from the available data. The usual method of generating gridded wind fields is to calculate an initial estimate of the field using interpolation of the observed winds followed by adjustment of the field, if desired.

This section of the report describes some of the common techniques use for interpolating winds and adjusting wind fields. Techniques involving transform functions (Lamb and Hati 1987), polynomial basis functions (Allwine and Whiteman 1985), and data assimilation (Yamada and Bunker 1988; Andren 1990) are not addressed because their computational requirements exceed HEDR Project resources. Pielke (1989) provides additional rationale for not considering data assimilation techinques by stating that determining an accurate initial state may be impossible.

Table 2-1. Time-integrated Air Concentrations for 1945(Ci-sec/m^3) based on 100 Realizations of the RATCHET Code.

	Percentile		
Node Name	10th	50th	90th
Arlington, OR	3.16e-5	4.71e-5	6.30E-5
Baker, OR	4.08e-6	7.90e-6	1.24e-5
Benton City, WA	1.85e-3	2.61e-3	4.37e-3
Bonners Ferry, ID	3.37e-5	4.28e-5	5.60e-5
Chelan, WA	1.03e-5	1.60e-5	2.67e-5
Colfax, WA	1.64e-4	2.18e-4	2.68e-4
Colville, WA	6.60e-5	8.20e-5	1.12e-4
Coeur d'Alene, ID	5.38e-5	6.71e-5	8.46e-5
Coulee City, WA	8.68e-5	1.17e-4	1.64e-4
The Dalles, OR	5.46e-6	1.03e-5	1.73e-5
Dayton, WA	1.85e-4	2.34e-4	3.10e-4
Ellensburg, WA	4.09e-5	5.80e-5	9.42e-5
Eltopia, WA	5.66e-3	7.08e-3	8.64e-3
Enterprise, OR	6.22e-6	1.02e-5	1.60e-5
Fossil, OR	3.59e-5	5.16e-5	7.80e-5
George, WA	9.69e-5	1.42e-4	1.93e-4
Harrington, WA	2.46e-4	3.00e-4	4.00e-4
Heppner, OR	1.79e-4	2.34e-4	3.14e-4
Irrigon, OR	7.28e-4	9.09e-4	1.20e-3
Kahlotus, WA	1.58e-3	1.89e-3	2.42e-3
Kennewick, WA	2.96e-3	3.58e-3	4.53e-3
LaCrosse, WA	4.06e-4	5.14e-4	6.49e-4
LaGrande, OR	1.68e-5	2.33e-5	3.44e-5
Lewiston, ID	5.96e-5	8.91e-5	1.32e-4
Madras, OR	4.48e-6	6.86e-6	1.02e-5
Meadows, ID	7.48e-7	1.57e-6	3.86e-6
Moses Lake, WA	2.74e-4	3.58e-4	5.33e-4
Newport, WA	9.50e-5	1.15e-4	1.42e-4
Omak, WA	9.94e-6	1.69e-5	2.90e-5
Orofino, ID	1.48e-5	2.15e-5	3.08e-5
Othello, WA	9.72e-4	1.24e-3	1.54e-3
Pasco, WA	3.70e-3	4.40e-3	5.38e-3
Pendleton, OR	3.96e-4	5.40e-4	6.38e-4
Richland, WA	6.42e-3	7.92e-3	9.66e-3
Ritzville, WA	6.12e-4	7.40e-4	9.48e-4
Sandpoint, ID	4.77e-5	5.97e-5	7.62e-5
Spokane, WA	1.70e-4	2.04e-4	2.53e-4
Sunnyside, WA	1.85e-4	2.52e-4	3.47e-4
Vantage, WA	2.27e-4	3.07e-4	4.07e-4
Walla Walla, WA	2.88e-4	4.02e-4	5.56e-4
Wenatchee, WA	1.06e-5	1.76e-5	2.77e-5
Wilbur, WA	8.44e-5	1.17e-4	1.62e-4
Yakima, WA	2.36e-5	4.05e-5	6.46e-5

2.7.1 Interpolation Methods The interpolation process involves adjusting the observed winds to standard heights, converting the winds from direction and speed to east-west and north-south

components, and interpolating to grid nodes. When wind data are available for several levels, the process is repeated at each level.

Wind directions are expressed in degrees and range from 0° (north) to 359° (1° west of north). As long as two wind directions are not too different, and not near north, the directions may be averaged with reasonable results. However, if the one direction is just west of north, say 355°, and the other is just east of north, say 005°, the result is near south (180°). As a result, horizontal interpolation of the winds is generally done using cartesian (east-west and north-south) components of the wind vector rather than wind direction and speed. The transformation from direction and speed to cartesian components is made using trignometric functions

$$u = -s \sin \theta$$

and

$$v = -s \cos \theta$$

where u is the east-west component of the vector (+ for transport to the east), v is the north-south component (+ for transport to the north), s is the wind speed, and θ is the wind direction.

Given the u and v wind components at reporting stations, the common method of obtaining an initial wind field estimate is interpolation using a weighted average,

$$C_{ij} = \sum_{k=1}^{n} C_k W_k(r) / \sum_{k\text{-}1}^{n} W_k(r) \qquad (1)$$

where C_{ij} is the wind component (either u or v) at grid node i,j, C_k is the observed wind component at the station k, n is the total number of stations, $W_k(r)$ is the weighting function, i and j are the grid increments, and r is the distance from the grid interpolation point to the station. This scheme is easy to implement and is widely used in applications where fast wind-field estimation is a priority.

Several methods have been proposed for determining the weights used in horizontal interpolation. Goodin et al. (1979) discuss both interpolation and weighting methods. Among the methods dicussed are $1/r^n$ weighting, and functions that use more complicated functions, such as exponentials and fitted polynomials. In general, weights are inversely related to the distance between node and the observation point.

The set of weighting factors in most common usage is simply

$$W_k(r) = \frac{1}{r^n} \qquad (2)$$

where n is 1, 2, or 3. This weighting scheme may be modified by establishing an arbitrarily assigned radius of influence, R and setting the weight to zero when the distance exceeds R (Wendell 1979; Goodin et al. 1980).

The usual value of n is 2. However, the choice of n should depend on the characteristics of the observing station. For example, when data are very sparse, such as upper-level data over a mesoscale region, a $1/r$ weighting can be used to obtain smooth variations in the wind field. On the other hand, use of $1/r^2$ or $1/r^3$ weighting increases the weight given to a wind observation near its measurement point and decreases the weight as other wind measurement points are approached. With a dense station network, using an exponential or $1/r^3$ may be more appropriate, to limit the radius of influence of each station and preserve sharp features such as fronts.

Figure 2-9 shows the variation of weights given to winds between two measurement points for $1/r$, $1/r^2$, and $1/r^3$ weighting. It shows that increasing n increases the weight given to measured winds near their measurement point. It also shows that increasing n decreases the region in which transitions take place. Note that all of these schemes give equal weights to winds from two stations at a point equidistant from the stations. Figure 2-10 shows an example of effect of two different weighting factors on transport fields derived from the same observed winds. The fields in the example are based winds observed at 15 PST from December 19, 1944. The field shown in Figure 2-10(a) was derived using $1/r$ weighting in Equation (1). Figure 2-10(b) shows the field derived using $1/r^2$ weighting.

Qualitatively, the wind fields appear nearly equivalent. In both cases, there is a region of nearly calm wind in the vicinity of the Hanford Site; there are relatively strong southeasterly winds near Pendleton; there are relatively strong easterly winds in the vicinity of

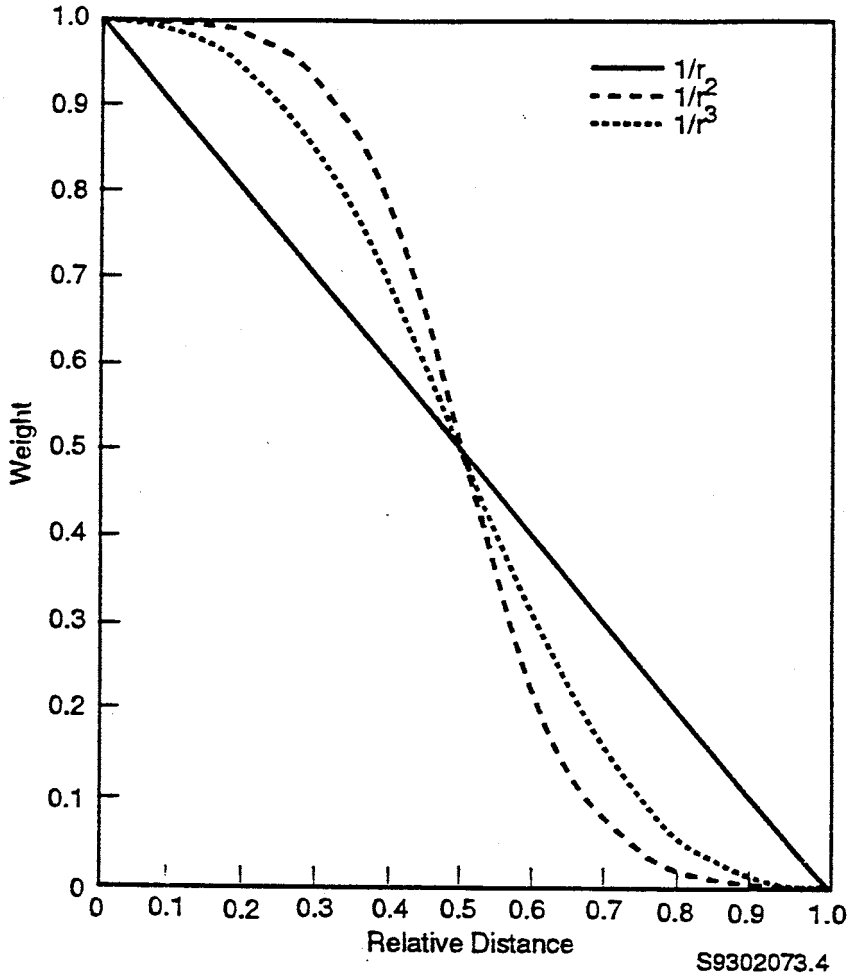

Figure 2-9. Interpolation Variations for Three Weighting Schemes

Spokane, and there are northerly winds along the western edge of the model domain. The primary difference between the wind fields is in the size of the low wind speed area near Hanford. The larger area in Figure 2-10(b) is caused by the additional weight that $1/r^2$ assigns to the HMS wind data in the vicinity of the station. Secondary differences, e.g., the smoothness of the spatial variations in the wind field, are also noticeable at the HMS.

Optimal interpolation is a more sophisticated interpolation scheme than the simple distance weighting schemes. It uses statistical correlations among stations in determining interpolation weights. As a result, optimal interpolation may identify and decrease the influence of unrepresentative observations. However, the statistical aspects of optimal interpolation require substantial analysis of climatological records. As a consequence, the operational mesoscale use of optimal interpolation has been quite limited. Although the interpolation scheme has been tested in

mesoscale regions by Cats (1980) and Johnson (1982), no use with a transport model has been reported.

2.7.2 Adjustment Techniques Wind fields generated using an interpolation technique are often used directly in transport and diffusion models (e.g. Ramsdell et al. 1983; Wang and Waldron 1990; Scire et al. 1984). However, there are cases where wind fields are adjusted to conserve the air mass within the model domain or fit the equations of motion. Three techniques are commonly used to perform these adjustments: mass consistent methods, transform methods, and data assimilation methods. Transform and data assimilation techniques are too computationally intensive to be used in the RATCHET code and are not discussed further.

One of the first questions raise about wind fields is: are they mass consistent? That is do they conserve mass? Note that the question specifically refers to the mass of the air in the model domain. Assuming that air is an incompressible fluid, a mass-consistent wind field is a wind field in which the continuity equation is satisfied at every point. With this assumption, the continuity equation is

$$\frac{\partial u}{\partial x}+\frac{\partial v}{\partial y}+\frac{\partial w}{\partial z}=0 \qquad (3)$$

where u, v and w are the wind components, x and y are the horizontal coordinates, and z is the vertical component. Diffusion models that compute concentrations using a two-dimensional flux equation require mass-consistent wind fields to conserve mass of the material being dispersed. This is not an issue in the HEDR Project because RATCHET implements a puff model in which the diffusion and depletion of material are treated independently of the transport.

However, adjustment of an initial wind field using a constraint based on the continuity equation has other potential benefits. For example, it can reduce the effects of small-scale features such as local terrain or short-lived weather disturbances (i.e. cumulus convection) on an interpolated regional wind field. These are the reasons for considering use of a mass-consistent wind field in RATCHET.

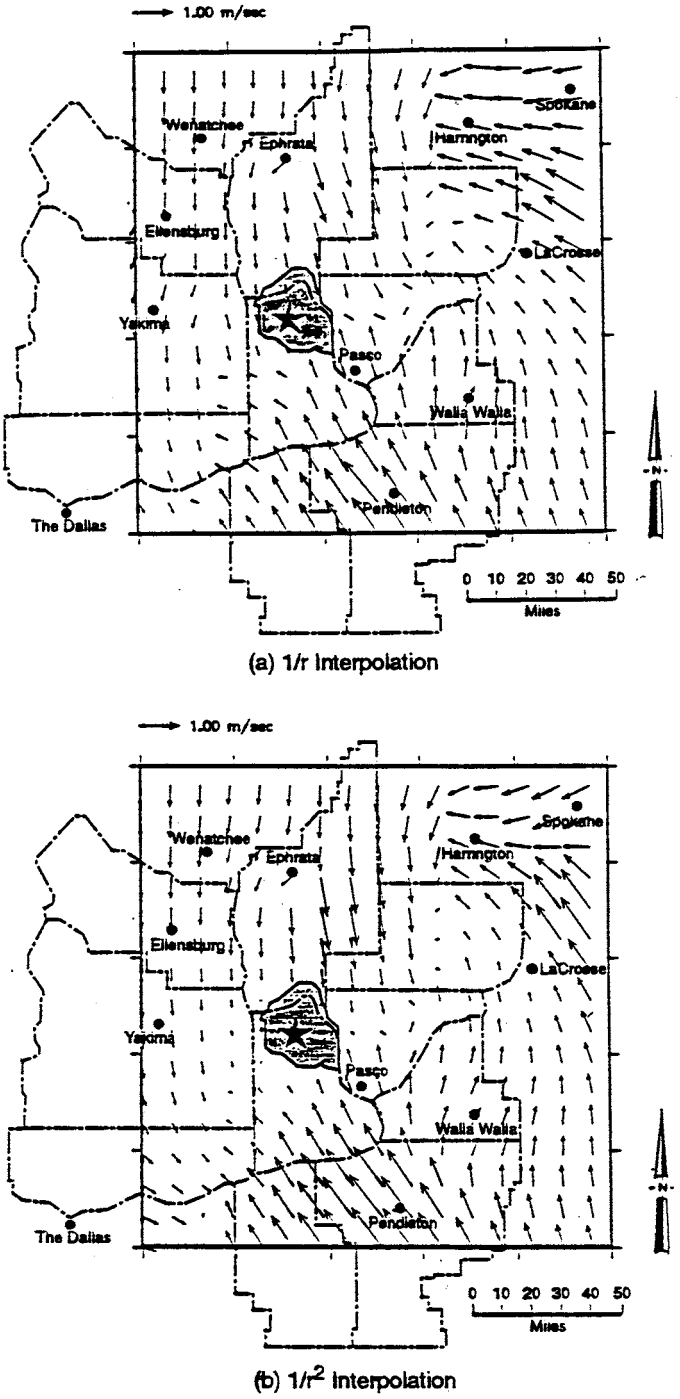

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Figure 2-10. Comparison of Wind Fields Using Two Weighting Schemes

The most popular method for acheiving mass consistency is the variational calculus approach originally applied to transport modeling by Sherman (1978). In this technique, an initial gridded wind field is changed by a minimal amount in an overall least squares sense, while assuring continuity of mass or some other dynamical constraint, such as conservation of vorticity. Ross et al. (1988), minimizes the equation

$$E(u,v,w) = \int\int\int \{\alpha_1^2 (u - u_0)^2 + \alpha_1^2 (v - v_0)^2 + \alpha_2^2 (w - w_0)^2\} dV \quad (4)$$

subject to the mass constraint given in Equation (3). In equation (4), V is a unit volume, u_o, v_o, and w_o are the initial interpolated horizontal and vertical wind components, and α_1 and α_2 are coefficients that determine the degree of adjustment to the initial wind field.

Equation (4) represents an estimate of the area-averaged kinetic energy difference between the initial wind field and the nondivergent adjusted wind field. Minimization of this equation ensures that changes to the wind field are made with a minimal impact on the overall wind energy. In regions of complex terrain, the solution of Equations (3) and (4) can be affected by terrain features. Sherman (1978) solved the minimization by assuming that the surface terrain followed a series of steps between grid points. However, this leads to large velocity errors at the surface as shown by Lewellen, et al. (1982). More recent implementations have used terrain following coordinates the produce in a smooth representation of terrain effects (Ross et al. 1988; Traci et al. 1978).

The main difficulty in using mass-consistent adjustment techniques is the number of free parameters that must be empirically or subjectively determined. Minimization of Equation (4) with a constraint based on Equation (3) requires a knowledge of the upper-level winds and the mixed-layer height or level of zero vertical motion. Data on upper-level winds are not available for the HEDR atmospheric model domain for the period of interest. As a result, they must be estimated from surface data. The height of the top surface must be estimated, and vertical velocities at the top surface must be specified. In general, vertical velocities at the top surface are not known, and are usually assumed to be equal to zero. In addition, it is necessary to estimate coefficients α_1 and α_2 in Equation 4.

The estimates of α_2 and α_1 influence the final wind field by controlling the relative changes in the wind components. If α_1 and α_2 are small, the imposed constraint has a relatively large impact on the final wind field. Conversely, if α_1 and α_2 are large, the initial winds are not strongly modified.

Finally, the ratio α_1/α_2 determines the relative amount of adjustment of the vertical wind component with respect to the horizontal winds.

The NOABL scheme for generating mass consistent wind fields (Traci, et al., 1978) was implemented in RATCHET to examine the effects on wind fields and code execution times. The implementation uses three atmospheric layers. It assumed zero initial vertical velocity and a mixed layer height of 1000 m. The upper-level winds were estimated by the average of the gridded wind components over the model domain.

Figure 2-11 illustrates the effects of α_1 and α_2 on wind fields. All three parts of the figure are based on wind data for 2100 PST, December 22, 1944. Figure 2-11(a) shows the initial wind field estimate based on $1/r^2$ interpolation of the data. Figures 2-11(b) and -11(c) show wind fields following modification by the NOABL adjustment scheme (Traci, et al. 1978). The only difference in the adjustment scheme used to generate Figures 2-11(b) and 2-11(c) is in the ratio of the parameters α_1 and α_2.

An α_1/α_2 ratio of 0.001, which qualitatively corresponds to unstable atmospheric conditions, was used to generate Figure 2-11(b). The wind directions in this figure show little change from the original $1/r^2$ field. In contrast, in Figure 2-11(c), the α_1/α_2 ratio is 1, which is more typical of neutral atmospheric conditions. The result is a noticeable change in wind directions in the southeast portion of the domain. Figures 2-11(b) and 2-11(c) both show smoother wind speed transitions than seen in Figure 2-11(a). The difference is particularly noticeable in the convergence zone near Pasco.

A variety of simple techniques have been devised to reduce the subjective treatment of the parameters α_1 and α_2. For example, Ross et al. (1988) used a simple Froude number approximation to estimate α_1/α_2. This approximation has the effect of including the atmospheric stability in their adjustment. Another approach was tried by Barnard, et al., (1987) who modeled flow in a small region (~4 km^2) of complex terrain. They used observed wind data to assist in selection of α_1/α_2.

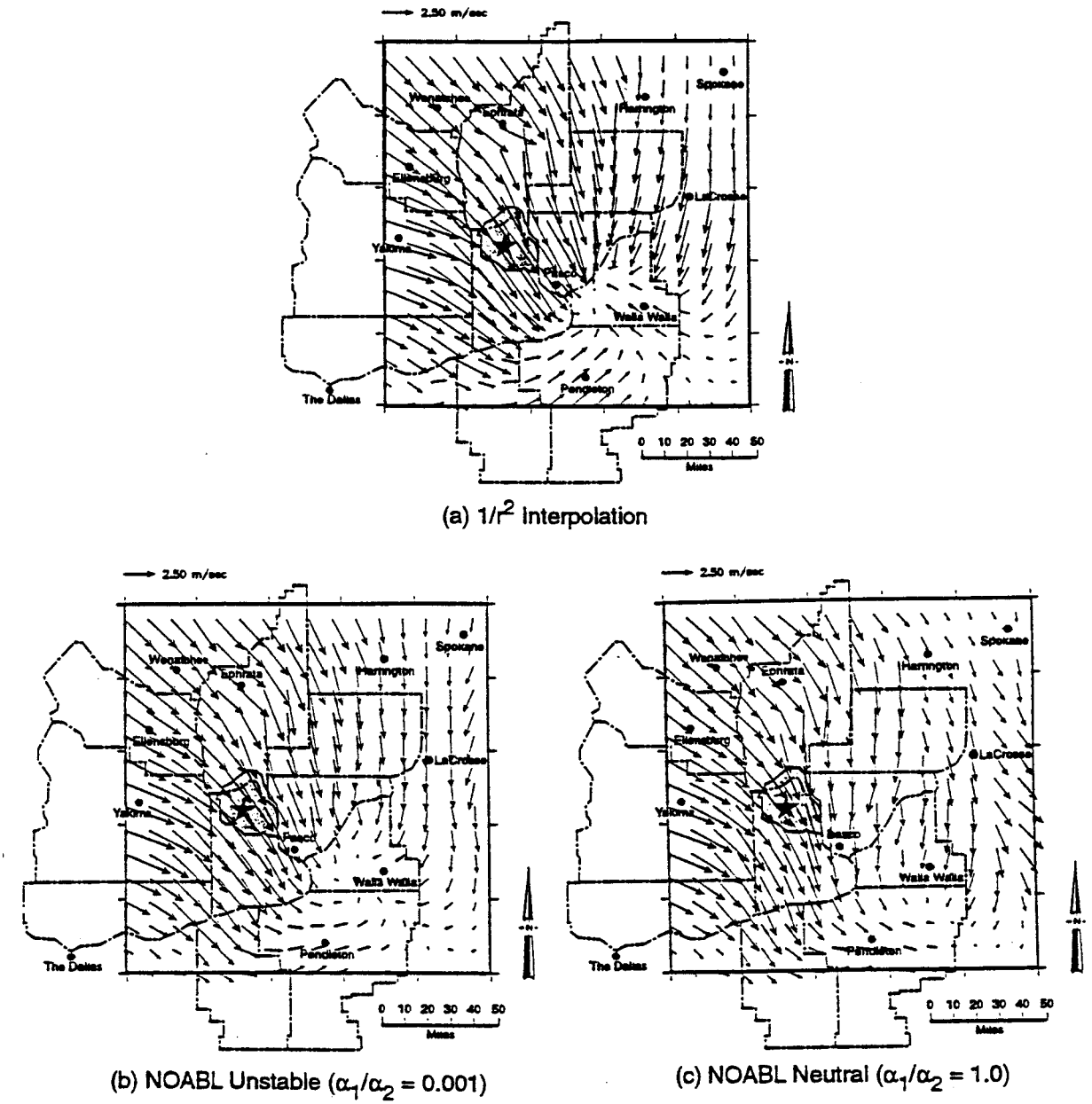

Figure 2-11. NOABL Adjustments to Estimated Wind Fields

Similarly, a variety of methods have been used to estimate the height of the top surface. King and Bunker (1984) and Goodin, et al. (1980) assigned values based on radiosonde observations of the boundary layer structure. Guo and Palutikof (1990) set the top surface using a climatological-based look-up table for night and day. Ultimately, the selection of the top surface depends on the number of observations available for a particular application. When observations are sparse, climatological values can be used with reasonable success (Guo and Palutikof 1990).

One of the significant problems associated with mass consistent techniques is the general lack of model verification for mesoscale applications. Dispersion model comparisons presented in Lewellen, et al. (1985) and Lewellen and Sykes (1985) do not show that models using mass-consistent wind fields are better than models using interpolated fields without adjustment. Limited testing is reported in King and Bunker (1984) where the transport and diffusion model described in Davis, et al. (1984) is applied at three different locations. Although reasonable model performance is demonstrated, the relative merit of adjusted wind fields over the original interpolated wind fields is not discussed. Walmsley, et al. (1990) compare the results of four complex terrain wind field models to each other and to a reference observation point. Again, the model results show good agreement with the observing stations, however, the number of observation points (3) was too small to test for interpolation accuracy. Other model evaluations, such as Mathur and Peters (1990) present resultant fields of vertical motion, which by definition should be reduced by the mass consistency requirement.

2.7.3 Horizontal Interpolation Of Winds

Various methods have been developed for interpolating winds from randomly spaced observation points to evenly-spaced nodes on a grid. Several of these methods have been described. RATCHET uses weighted interpolation with $1/r^2$ weighting. This is one of the common methods, if not the most common method of weighting. No other single interpolation method has replaced the $1/r^2$ weighted averaging method in common usage.

Differences among hourly wind fields that result from differences in interpolation methods are generally small. Figure 2-10 showed an example of changes resulting from weighting. The HEDR system of codes accounts for uncertainties in release times that are of the order of 8 hours. The changes in wind fields associated with passing weather systems and diurnal thermal effects over this period are larger than the differences in wind fields associated with interpolation methods. Therefore, it is our recommendation that $1/r^2$ weighted averaging continue to be used for horizontal interpolation of winds in RATCHET.

2.7.4 Wind Field Adjustments

The review of wind field adjustment techniques indicates that the techniques usually require more information than is readily available for the HEDR atmospheric model domain for the period of interest. Undocumented experiences with a wind field model based on the code of Allwine and Whiteman (1985) indicate that the use of transform methods for calculation of wind fields requires more time than can reasonably be allotted for wind field calculations in RATCHET. Data assimilation techniques for adjusting wind field have been dismissed from consideration for the same reason. For example, a typical 24 hour model run requires roughly 53 minutes of Cray XMP computer time (Geai, et al. 1988). Design specifications for the RATCHET code (Ramsdell and Burk 1992, p. 4.1) established requirement that RATCHET execution take no more than 1 s per hour of real time simulation.

Two mass consistent wind field adjustment algorithms (Traci et al. 1978; Mathur and Peters 1990) have been implemented in modified versions of RATCHET for evaluation. These algorithms use different methods of adjustment of the wind field. Under most conditions the differences among the initial wind fields generated by $1/r^2$ weighted averaging and the adjusted fields are small. See Figure 2-11(c) for an example of the relatively large changes. However, there are significant differences in the time required for program execution. When the wind field adjustment algorithm proposed by Mathur and Peters is used, RATCHET execution takes more than twice as long as execution with only $1/r^2$ interpolation. The algorithm proposed by Traci et al. increases RATCHET execution time by almost a factor of 3.

Calculations with the RATCHET code indicate that the execution speed design criteria can be met even using a mass consistent wind field adjustment algorithm. The question then becomes whether there is sufficient value added by mass consistent algorithm to justify the additional computational time.

Dispersion model evaluations involving short releases (Lewellen et al., 1982; Lewellen and Sykes 1985; Lewellen et al., 1986; Weber et al., 1987; Klug et al., 1992) have failed to find that models using wind fields adjusted for mass-consistency produce better concentration predictions than models that use interpolated wind fields without adjustment. Weber et al. (1984) suggest that correct treatment of wind fields is less important in estimating long-term concentrations than it is in estimating short-term concentrations. The same suggestion is offerred by Carhart et al. (1989).

Mass consistent wind fields have not been demonstated to have value in estimating short-term concentrations. The relatively small range of time-integrated air concentrations calculated for 1945 shown in Table 2-1 given the uncertainties in model input would indicate that mass consistent wind fields would be of less value in estimating long-term concentrations than they are in estimating short-term concentrations. Unless future model evaluation studies offer positive evidence that the additional computational time required to adjust wind fields for mass consistency improves model performance in predicting concentrations it is not warranted in RATCHET. Therefore, we recommend that RATCHET continue to rely on interpolated wind fields for transport calculations.

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3. HEDR Source Term Estimates

The National Research Council committee review (NRC 2000) of the HTDS draft final report repeated the concern of Hoffman et al. (1999) that portions of the ^{131}I source term could have been underestimated. According to the NRC report, the main points raised by the Hoffman et al. report are

- The HEDR project estimates of the amounts of 131I processed and released in 1959 and 1960 are substantially less than the amounts reported by Warren (1961), which are the source of HEDR release estimates.
- The HEDR project documents use Warren (1961) as a source but do not evaluate the credibility of his values; for example, he projected an unrealistically high scrubber efficiency.
- The HEDR project misapplied measured release-factor data from 1959-1960 to the period 1951-1957, when less emission-control equipment was in place.
- The HEDR project incorrectly accounted for operation of the silver reactors in the B and T plants by inexperienced personnel during the first 18 months after installation in 1951.
- The HEDR project substantially underestimated the source-term uncertainties for the B, T, and REDOX plants.
- The HEDR project inadvertently used the medians instead of the arithmetic means of the monthly source terms for the air-concentration and ground-deposition calculations.
- The HEDR project did not propagate the source-term uncertainties to air concentrations, ground deposition, and doses.

These can be summarized as four main questions:

- Have errors in the published source term affected the HEDR or HTDS dose estimates?
- Is the HEDR source term consistent with the data from Warren (1961) for the period 1959 - 1960?
- Does the HEDR source term underestimate the releases in the 1950s and 1960s?
- Are uncertainties in the source term appropriately propagated throughout the following parts of the calculation?

3.1 Use of median versus mean monthly source terms

Hoffman et al. (1999) discovered an error in the monthly source terms published in C.M. Heeb 1994. *Radionuclide Releases to the Atmosphere from Hanford Operations, 1944 – 1972*, PNWD-2222 HEDR. Heeb indicated that the tabulated values of the data were means, and the calculations subsequently performed assumed them to be means. Table B.1 as published in PNWD-2222 HEDR contained the error, starting in August of 1951, of using a median rather than a mean release factor for ^{131}I. This caused an underestimation in the reported source term for the remaining months of a factor ranging from around 1.25 to 3.0, depending on which emitting facility was in operation at the time. The corrected table is presented as Table 3-1. This table has been available on the Internet since November 1999 at the address http://www.pnl.gov/eshs/cap/hra/pub/hedr.html . The subsequent data files used in the dose calculations have also been corrected. As a result, the HEDR DESCARTES computer program was rerun and an updated environmental concentration database (used as input to the CIDER computer code) was issued to Centers for Disease Control and Prevention and to the Washington State Department of Health. Because the corrections apply only for times after August 1951, these corrections have essentially no impact on published HEDR reports (for which representative doses were reported for 1944 through 1951 - releases for all of 1951 are increased by about 25%). The estimated overall release of ^{131}I from the Hanford Site increases by about 3% when this error is integrated from 1944 through 1972.

3.2 Considerations of the I-131 Releases Reported by J.H. Warren (1961)

It has been suggested that the data in the report by Warren (1961) used by Heeb (1994) to estimate radionuclide release fractions from the REDOX and PUREX facilities do not agree with the releases ultimately prepared by Heeb (1994). It has been further suggested that there may be an error in Heeb's estimates, since the final release estimates do not "replicate the data used to generate them." (Paraphrased by this author).

The presentation of tons of fuel processed through the REDOX and PUREX facilities in Heeb (1994, Table A.3) appears to be accurate. This information is corroborated in Roberts et al. (1992), Jenkins and Foster (1978), Gydesen (1992a), and Gydesen (1992b). It has most recently been heavily reviewed in the development of the Hanford Defined Wastes model and Hanford Best Basis Inventory (Kupfer et al. 1999). Kupfer et al. (1999) have made adjustments to Heeb's database to account for minor variations in the processing after 1966 (primarily to account for

Table 3-1. Estimated Monthly Releases to the Atmosphere from Separations Plant Operations 1944-1972 (Ci/month)

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1944	Dec	2360	2140							2140
1945	Jan	1350	1220							1220
1945	Feb	2350	2130							2130
1945	Mar	2300	2080							2080
1945	Apr	19900	18000	11800	10700					28700
1945	May	38600	34900	43700	39500					74500
1945	Jun	24600	22200	26800	24200					46500
1945	Jul	25900	23400	26100	23600					47000
1945	Aug	42400	38400	37200	33700					72100
1945	Sep	42700	38700	55300	50000					88700
1945	Oct	49500	44800	52200	47300					92100
1945	Nov	18200	16500	23500	21300					37800
1945	Dec	21100	19100	47800	43300					62300
1946	Jan	2340	2120	10600	9630					11800
1946	Feb	2960	2680	5210	4720					7400
1946	Mar	2310	2090	6480	5860					7950
1946	Apr	5730	5180	7180	6500					11700
1946	May	4760	4310	9910	8970					13300
1946	Jun	172	156	4930	4460					4620
1946	Jul	966	874	5170	4680					5560
1946	Aug	93	84	9460	8560					8650
1946	Sep	523	473	7950	7200					7670
1946	Oct	485	439	4840	4380					4820
1946	Nov	2280	2060	3830	3460					5520
1946	Dec	2170	1960	6010	5440					7400
1947	Jan	1850	1670	4960	4490					6160
1947	Feb	2490	2260	1740	1580					3830
1947	Mar	2190	1980	4020	3640					5620
1947	Apr	2220	2010	3150	2850					4850
1947	May	1970	1780	2430	2200					3990
1947	Jun	862	780	965	873					1650
1947	Jul	1150	1040	1390	1260					2300
1947	Aug	512	464	873	790					1250
1947	Sep	530	480	805	729					1210
1947	Oct	339	307	202	183					490
1947	Nov	174	157	133	120					278
1947	Dec	194	176	113	102					278
1948	Jan	45	41	196	178					219
1948	Feb	114	103	196	177					280
1948	Mar	105	95	81	74					168
1948	Apr	180	162	65	59					221
1948	May	95	27	14	4					31
1948	Jun	67	19	85	24					43
1948	Jul	192	55	284	81					135

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1948	Aug	286	81	223	63					145
1948	Sep	197	56	223	63					119
1948	Oct	279	79	320	91					170
1948	Nov	323	81	289	72					153
1948	Dec	327	82	299	75					156
1949	Jan	435	109	350	88					196
1949	Feb	363	91	48	12					103
1949	Mar	719	180	245	61					241
1949	Apr	255	64	264	66					130
1949	May	284	71	277	69					140
1949	Jun	148	37	168	42					79
1949	Jul	207	52	171	43					94
1949	Aug	273	68	72	18					86
1949	Sep	277	69	282	71					140
1949	Oct	257	64	311	78					142
1949	Nov	239	60	165	41					101
1949	Dec	28700	7180	255	64					7240
1950	Jan	183	46	184	46					92
1950	Feb	160	40	168	42					82
1950	Mar	240	60	240	60					120
1950	Apr	240	60	182	46					105
1950	May	259	65	240	60					125
1950	Jun	146	37	259	65					101
1950	Jul	552	138	411	103					241
1950	Aug	3350	839	2800	701					1540
1950	Sep	2480	620	2700	676					1300
1950	Oct	1480	369	1940	485					854
1950	Nov	961	240	1190	15					255
1950	Dec	2190	548	1620	20					568
1951	Jan	6520	65	1160	12					77
1951	Feb	4060	41	4630	46					87
1951	Mar	5470	109	11900	237					346
1951	Apr	25000	1250	22900	1140					2390
1951	May	40400	5330	33400	4410					9740
1951	Jun	39200	4890	13900	1730					6620
1951	Jul	20700	2490	13200	1580					4070
1951	Aug	41300	1400	32500	1100					2500
1951	Sep	27200	922	24900	844					1770
1951	Oct	31000	1050	41300	1400					2450
1951	Nov	30300	1030	47600	1610					2640
1951	Dec	27700	939	21600	732					1670
1952	Jan	51300	1740	34200	1160	1770	60			2960
1952	Feb	19500	661	30000	1020	11000	373			2050
1952	Mar	43600	1480	9410	319	21000	712			2510
1952	Apr	22600	766	1570	53	43400	1470			2290
1952	May	10100	342	533	18	34900	1180			1540
1952	Jun	198	7	895	30	16900	573			610
1952	Jul	4010	136			4750	161			297

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1952	Aug	6350	215			11000	373			588
1952	Sep	131	4			9800	332			337
1952	Oct	142	5			3130	106			111
1952	Nov	1040	35			5830	198			233
1952	Dec	8240	279			1300	44			323
1953	Jan	102	3			6340	215			218
1953	Feb	655	22			994	34			56
1953	Mar	744	25			3320	113			138
1953	Apr	6320	214			6840	232			446
1953	May	3790	128			6730	228			357
1953	Jun	7290	247			6950	236			483
1953	Jul	11600	393			19400	658			1050
1953	Aug	3370	114			9210	312			426
1953	Sep	2700	92			6210	211			302
1953	Oct	2720	92			17800	603			696
1953	Nov	5200	176			541	18			195
1953	Dec	865	29			9990	339			368
1954	Jan	11000	373			4640	157			530
1954	Feb	1310	44			2280	77			122
1954	Mar	651	22			4540	154			176
1954	Apr	554	19			3310	112			131
1954	May	3520	119			5570	189			308
1954	Jun	1640	56			3730	126			182
1954	Jul	1610	55			656	22			77
1954	Aug	2120	72			821	28			100
1954	Sep	3430	116			2060	70			186
1954	Oct	7730	262			132	4			267
1954	Nov	1630	55			60	2			57
1954	Dec	2270	77			863	29			106
1955	Jan	1610	55			416	14			69
1955	Feb	2280	77			5320	180			258
1955	Mar	182	6			17000	576			582
1955	Apr	2750	93			51	2			95
1955	May	2360	80			0	0			80
1955	Jun	843	29			2310	78			107
1955	Jul	751	26			2040	69			95
1955	Aug	0	0			1580	54			54
1955	Sep	1570	53			4640	157			211
1955	Oct	1300	44			4230	143			187
1955	Nov	193	7			27	1			7
1955	Dec	22	1			2210	75			76
1956	Jan	1	0			470	16	15	0	16
1956	Feb					1310	44	4	0	44
1956	Mar					295	10	10	0	10
1956	Apr					78	3	2260	6	8
1956	May					1840	62	230	1	63
1956	Jun					1290	44	5530	14	58
1956	Jul					141	5	44	0	5

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1956	Aug					99	3	219	1	4
1956	Sep					68	2	1250	3	5
1956	Oct					36	1	803	2	3
1956	Nov					203	7	2550	6	13
1956	Dec					1310	44	1560	4	48
1957	Jan					254	9	1220	3	12
1957	Feb					457	16	748	2	17
1957	Mar					182	6	714	2	8
1957	Apr					681	23	1490	4	27
1957	May					547	19	1210	3	22
1957	Jun					286	10	1360	3	13
1957	Jul					818	28	2400	6	34
1957	Aug					1130	38	2670	7	45
1957	Sep					1480	50	2120	5	56
1957	Oct					1740	59	5880	15	74
1957	Nov					2850	97	7420	19	115
1957	Dec					5610	190	9660	24	214
1958	Jan					1450	49	13500	34	83
1958	Feb					9240	313	33500	84	397
1958	Mar					5420	184	25400	64	247
1958	Apr					4300	146	19900	50	196
1958	May					8570	291	19900	50	340
1958	Jun					3210	109	1150	3	112
1958	Jul					2770	94	7190	18	112
1958	Aug					1900	64	3260	8	73
1958	Sep					1740	59	10800	27	86
1958	Oct					0	0	7600	19	19
1958	Nov					0	0	15000	38	38
1958	Dec					0	0	12400	31	31
1959	Jan					0	0	9830	25	25
1959	Feb					0	0	5040	13	13
1959	Mar					0	0	7620	19	19
1959	Apr					0	0	5400	14	14
1959	May					0	0	7690	19	19
1959	Jun					8	0	13500	34	34
1959	Jul					2	0	3870	10	10
1959	Aug					4	0	12800	32	32
1959	Sep					0	0	19200	48	48
1959	Oct					2	0	10200	26	26
1959	Nov					71	2	6840	17	20
1959	Dec					0	0	10900	27	27
1960	Jan					8	0	37800	95	95
1960	Feb					64	2	9990	25	27
1960	Mar					19	1	1400	4	4
1960	Apr					50	2	4090	10	12
1960	May					4	0	5070	13	13
1960	Jun					14	0	1240	3	4
1960	Jul					4	0	6620	17	17

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1960	Aug					102	3	25500	64	67
1960	Sep					0	0	2090	5	5
1960	Oct					0	0	8	0	0
1960	Nov					0	0	5620	14	14
1960	Dec					0	0	14900	37	37
1961	Jan					0	0	4620	12	12
1961	Feb					0	0	5270	13	13
1961	Mar					14	0	4980	13	13
1961	Apr					1	0	1560	4	4
1961	May					0	0	3340	8	8
1961	Jun					0	0	4990	13	13
1961	Jul					15	0	2440	6	7
1961	Aug					54	2	5530	14	16
1961	Sep					59	2	3390	8	11
1961	Oct					104	4	3960	10	13
1961	Nov					390	13	2010	5	18
1961	Dec					5	0	80	0	0
1962	Jan					488	17	371	1	18
1962	Feb					300	10	130	0	11
1962	Mar					46	2	42	0	2
1962	Apr					0	0	22	0	0
1962	May					2	0	106	0	0
1962	Jun					5	0	167	0	1
1962	Jul					1	0	723	2	2
1962	Aug					2	0	380	1	1
1962	Sep					0	8	4	0	8
1962	Oct					0	0	222	1	1
1962	Nov					0	0	266	1	1
1962	Dec					0	0	2470	6	6
1963	Jan					0	0	0	0	0
1963	Feb					0	0	104	0	0
1963	Mar					0	0	500	1	1
1963	Apr					32	1	225	1	2
1963	May					4	0	456	1	1
1963	Jun					53	2	359	1	3
1963	Jul					0	0			0
1963	Aug					0	0	108	0	0
1963	Sep					0	0	209	72	72
1963	Oct					4	0	95	0	0
1963	Nov					0	0	70	0	0
1963	Dec					0	0	210	1	1
1964	Jan					0	0	159	0	0
1964	Feb					0	0	42	0	0
1964	Mar							322	1	1
1964	Apr					0	0	316	1	1
1964	May					0	0	624	2	2
1964	Jun					20	1	306	1	1
1964	Jul					0	0	206	1	1

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1964	Aug					0	0	1110	3	3
1964	Sep					0	0	0	0	0
1964	Oct					0	0	1330	3	3
1964	Nov					0	0	969	2	2
1964	Dec					1	0	57	0	0
1965	Jan					1	0	52	0	0
1965	Feb					2	0	41	0	0
1965	Mar					8	0	86	0	1
1965	Apr					25	1	21	0	1
1965	May					109	4	250	1	4
1965	Jun					3	0	27	0	0
1965	Jul					28	1	27	0	1
1965	Aug					20	1	60	0	1
1965	Sep					4	0	29	0	0
1965	Oct					0	0	497	1	1
1965	Nov					1	0	40	0	0
1965	Dec					0	0	658	2	2
1966	Jan					2	0	1470	4	4
1966	Feb					0	0	7	0	0
1966	Mar					3	0	167	0	1
1966	Apr					0	0	793	2	2
1966	May					3	0			0
1966	Jun					239	8			8
1966	Jul					54	2			2
1966	Aug					7	0	0	0	0
1966	Sep					1	0	1	0	0
1966	Oct					0	0	167	0	0
1966	Nov					0	0	0	0	0
1966	Dec							0	0	0
1967	Jan							137	0	0
1967	Feb							69	0	0
1967	Mar							248	1	1
1967	Apr							0	0	0
1967	May							166	0	0
1967	Jun							0	0	0
1967	Jul							0	0	0
1967	Aug							10	0	0
1967	Sep							3	0	0
1967	Oct							0	0	0
1967	Nov							3	0	0
1967	Dec							0	0	0
1968	Jan							0	0	0
1968	Feb							0	0	0
1968	Mar							1	0	0
1968	Apr							4	0	0
1968	May							1	0	0
1968	Jun							1	0	0
1968	Jul							0	0	0

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1968	Aug							2	0	0
1968	Sep							0	0	0
1968	Oct							2	0	0
1968	Nov							0	0	0
1968	Dec							0	0	0
1969	Jan							0	0	0
1969	Feb							0	0	0
1969	Mar							0	0	0
1969	Apr							0	0	0
1969	May							0	0	0
1969	Jun							0	0	0
1969	Jul							0	0	0
1969	Aug							0	0	0
1969	Sep							0	0	0
1969	Oct							0	0	0
1969	Nov							0	0	0
1969	Dec							0	0	0
1970	Jan							1	0	0
1970	Feb							0	0	0
1970	Mar							0	0	0
1970	Apr							0	0	0
1970	May							0	0	0
1970	Jun									
1970	Jul									
1970	Aug									
1970	Sep									
1970	Oct									
1970	Nov									
1970	Dec									
1971	Jan									
1971	Feb									
1971	Mar							0	0	0
1971	Apr							0	0	0
1971	May							0	0	0
1971	Jun							0	0	0
1971	Jul							0	0	0
1971	Aug							0	0	0
1971	Sep							0	0	0
1971	Oct									
1971	Nov									
1971	Dec									
1972	Jan									
1972	Feb							0	0	0
1972	Mar							0	0	0
1972	Apr									
1972	May									
1972	Jun									
1972	Jul									

Year	Month	T Plant Processed	T Plant Released	B Plant Processed	B Plant Released	REDOX Processed	REDOX Released	PUREX Processed	PUREX Released	All Released
1972	Aug									
1972	Sep									
1972	Oct									
1972	Nov									
1972	Dec									
Total		939882	339548	789167	407650	391835	13288	508075	1343	762015

aluminum- versus zirconium-clad fuels and to introduce other non-Hanford-origin fuel sources), but none to the time period in question.

Calculation of releases requires the conversion of tons processed through each facility, the average holdup (cooling time) of the fuel, and the power level of the reactor(s) that produced it, into the quantity of iodine-131 in the fuel at the time of dissolving. Heeb (1994) provides all of these required pieces of information on a monthly average basis. Warren (1961) does not provide the quantities of fuel processed that resulted in the reported releases.

Probably the most important point, corroborated by Heeb (1994), Gydesen (1992a,b), Roberts et al. (1992), Jenkins and Foster (1978), and others, is that no daily information exists for this time period. (See specifically Gydesen (1992b, page 3.8, paragraph 3) – the daily records are reported to have been destroyed.) *The Warren report appears to be an exception to this statement*, except that the information is partial and therefore cannot be corroborated with other sources.

Warren's information was used by Heeb only to estimate the fractional release of radioiodine from the facilities. Not enough data are provided on source and quantity of fuel to allow it to be used in the modeling; therefore it was not a direct input to the release estimates made using the release fraction. However, the releases reported in Warren are parallel to those presented in other sources, particularly the monthly reports issued by the staff of the Hanford Radiation Protection Operation. It is apparent from the raw data of Warren and the compiled data of these reports that both used the same sources. The values derived from Warren's figures and those in the monthly reports for 1959 and 1960 are essentially identical (see Table 3-2). If the releases and release fractions estimated based on Warren's work are assumed to be valid, then their basis also supports the idea that, at least during this time period, the monitoring results are also valid.

The daily information on burnup in processed fuel in Warren (1961) is compatible with the monthly averages given in Heeb (1994), if it is assumed that the individual daily listings (and not the longer clusters) correspond to 1 to 3 dissolver batches per day of about 1 ton each.

Radioactive decay is not a linear process; it is exponential. Therefore, the average holdup is not the best descriptor for evaluating radioactive decay. One ton of fuel cooled for 100 days, mixed with 99 tons of fuel cooled for 201 days, provides 100 tons cooled an average of 200 days. However, the release of radioiodine from the 1 ton of 100-day material will be about 60 times

greater than the combined release of the other 99 tons. This general problem appears to be the basis of the discrepancy when the Warren values for 1959-1960 are compared to Heeb's; Warren had access to detailed daily information (which no longer exists) about the fuel, and only reported the releases from the short-cooled material. The age of this short-cooled fuel was sufficiently less than the average to make the estimates of total release from all of the fuel appear to be in error.

Heeb (1994) used a mass-balance model to account for all the fuel from all the reactors through all the processing plants. To a large extent, the model assumes that the first fuel to be irradiated is the first fuel to be processed, since the daily records are not available. Due to the lack of necessary information, recreating the fine structure within a month, such as fuel processing "out of order", could not be done by HEDR. (Some detail has been added for the period after 1966 by Kupfer et al. 1999). Because the focus of HEDR was the early period (1944-1951) at the direction of the HEDR Technical Steering Panel, extended to 1957 to support the Fred Hutchinson Cancer Research Center's Hanford Thyroid Disease Study, and releases are documented to have been much lower in the 1958-1972 period, refinements for the later years were not considered to be warranted.

Only the total emissions from all separations plants are significant to doses beyond the Hanford site boundary. Table 3-2 lists various reported total releases for the time period in question. Releases are presented from HEDR, Warren, and Hanford Site monthly and annual reports (identified by HW- number). The values quoted here for Heeb (1994) are those revised using the mean release factor, rather than the median as originally reported. Figures 3-1 and 3-2 illustrate the release estimates of Heeb compared with the releases reported by the Hanford environmental monitoring group. Figure 3-1 is the data plotted linearly, and Figure 3-2 is the same data plotted logarithmically.

A close reading of Heeb, Table A.3, shows that beginning in November 1958, REDOX began processing primarily long-cooled, enriched-uranium fuels. Only smaller batches of natural uranium fuels were occasionally processed. Some of these smaller batches (but not all) correspond to the times that Warren reports non-negligible iodine releases. If these batches were to have shorter cooling times, it is not likely that they would cause the overall average cooling time to be greatly reduced.

The largest discrepancy between Heeb and Warren occurs in the period of September to October 1960. Warren's detailed dissolver-charging records (reproduced here as Figure 3-3)

Table 3-2. Monthly Releases of ^{131}I to the Atmosphere as Reported by Various Sources

	Updated PNWD-2222 HEDR			Warren			Results from historical reports (As 30x daily or 4x weekly reported)				Anderson
	REDOX Ci/month	PUREX Ci/month	Totals Ci/month	REDOX Ci/month	PUREX Ci/month	Totals Ci/Month	REDOX Ci/month	PUREX Ci/month	Totals Ci/month	HW Report	(1974) Ci/year
Jan-59	0.01	24.60	24.60	0.1	19.0	19.1	0.1	14.0	14.0	HW-59092	-
Feb-59	0.00	12.60	12.60	0.1	15.1	15.2	0.1	20.0	20.0	HW-59454	-
Mar-59	0.00	19.10	19.10	0.1	12.2	12.3	0.1	13.0	13.0	HW-59918	-
Apr-59	0.00	13.50	13.50	8.6	24.6	33.2	4.8	24.4	29.2	HW-60413	-
May-59	0.01	19.20	19.20	9.5	21.5	31.0			35.2	HW-60642	-
Jun-59	0.27	33.80	34.00	2.9	25.7	28.6			24.8	HW-61441	-
Jul-59	0.08	9.68	9.75	6.2	9.8	16.0			14.3	HW-61441	-
Aug-59	0.12	32.00	32.10	1.7	27.4	29.1			21.6	HW-61826	-
Sep-59	0.01	48.00	48.00	6.6	21.3	27.9	7.2	11.6	18.8	HW-62277	-
Oct-59	0.08	25.50	25.60	4.6	13.4	18.0	4.4	18.4	22.8	HW-62699	-
Nov-59	2.41	17.10	19.50	13.6	16.8	30.4	12.4	16.8	29.2	HW-63179	-
Dec-59	0.00	27.30	27.30	12.8	23.5	36.3	11.6	20.8	32.4	HW-63557	-
Annual totals			285.25	Annual totals		297.2	Annual totals		275.3		289
				HW-64371		296.0					
Jan-60	0.28	94.50	94.80	1.4	23.5	24.9	1.5	34.0	35.0	HW-63920	-
Feb-60	2.18	25.00	27.20	0.7	20.1	20.8	0.7	18.0	19.0	HW-64253	-
Mar-60	0.64	3.50	4.14	6.1	7.1	13.2	0.6	5.5	6.1	HW-64757	-
Apr-60	1.71	10.20	11.90	5.5	15.0	20.5	5.8	15.0	21.0	HW-65154	-
May-60	0.14	12.70	12.80	1.3	15.5	16.8	2.9	16.0	19.0	HW-65613	-
Jun-60	0.48	3.10	3.58	4.0	6.7	10.7	5.3	10.0	15.0	HW-66009	-
Jul-60	0.14	16.60	16.70	60.4	22.4	82.8	61.0	21.0	82.0	HW-66420	-
Aug-60	3.46	63.80	67.20	9.2	43.2	52.4	8.0	44.0	51.0	HW-66778	-
Sep-60	0.00	5.23	5.23	9.3	43.8	53.1	9.4	44.0	53.0	HW-67060	-
Oct-60	0.00	0.02	0.02	0.3	6.2	6.5	0.3	4.9	5.2	HW-67439	-
Nov-60	0.00	14.10	14.10	0.1	23.3	23.4	0.1	24.0	24.0	HW-67752	-
Dec-60	0.00	37.30	37.30	0.0	39.0	39.0	0.0	38.0	38.0	HW-68127	-
Annual totals			294.97	Annual totals		364.2	Annual totals		368.3		351

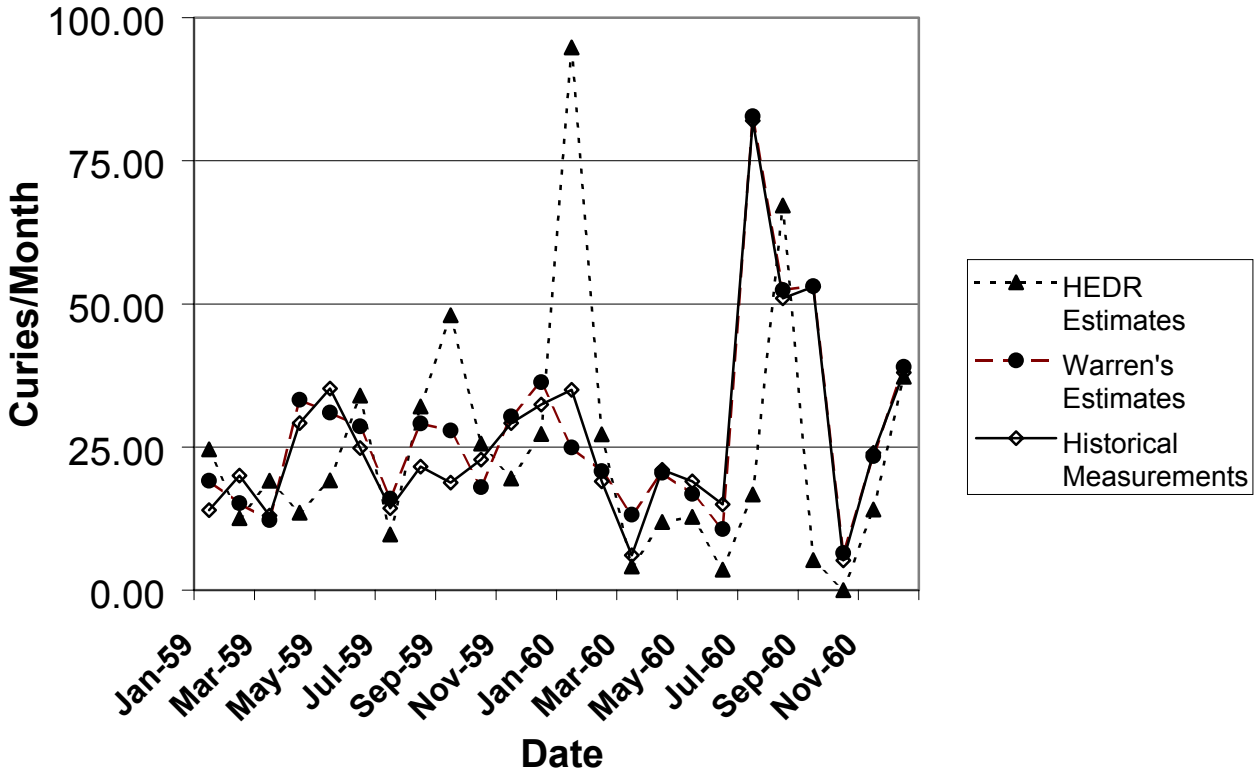


Figure 3-1. Comparison of releases reported by Heeb, Warren, and contemporaneous Hanford authors (linear scale).

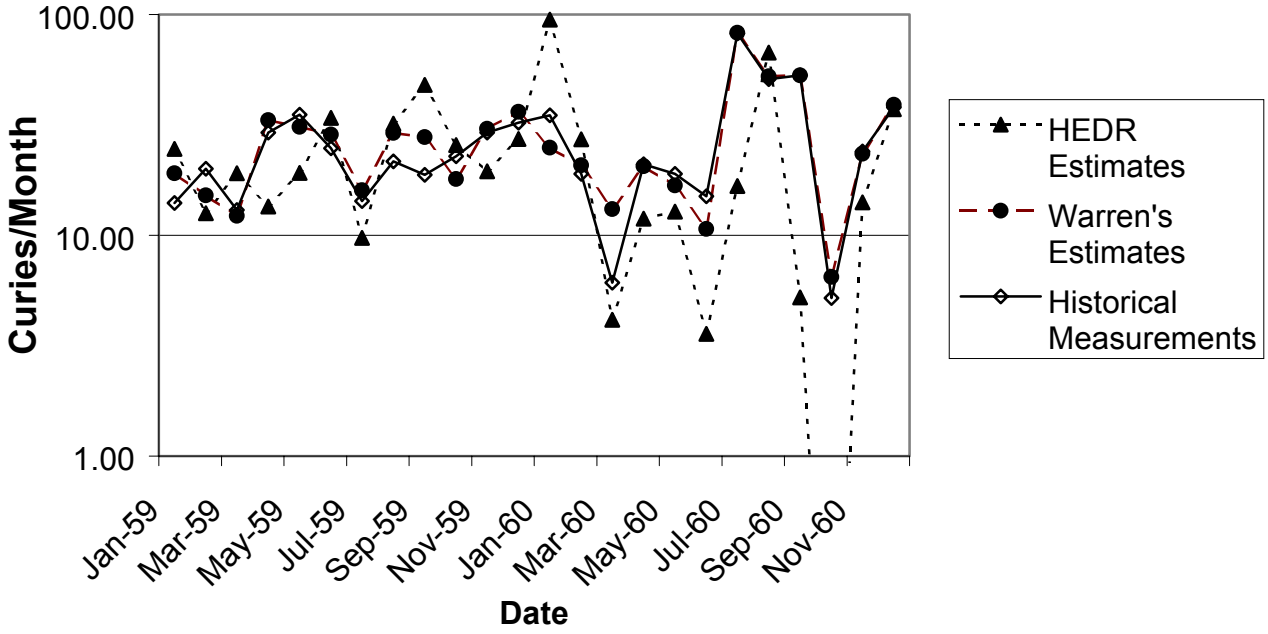


Figure 3-2. Comparison of releases reported by Heeb, Warren, and contemporaneous Hanford authors (logarithmic scale).

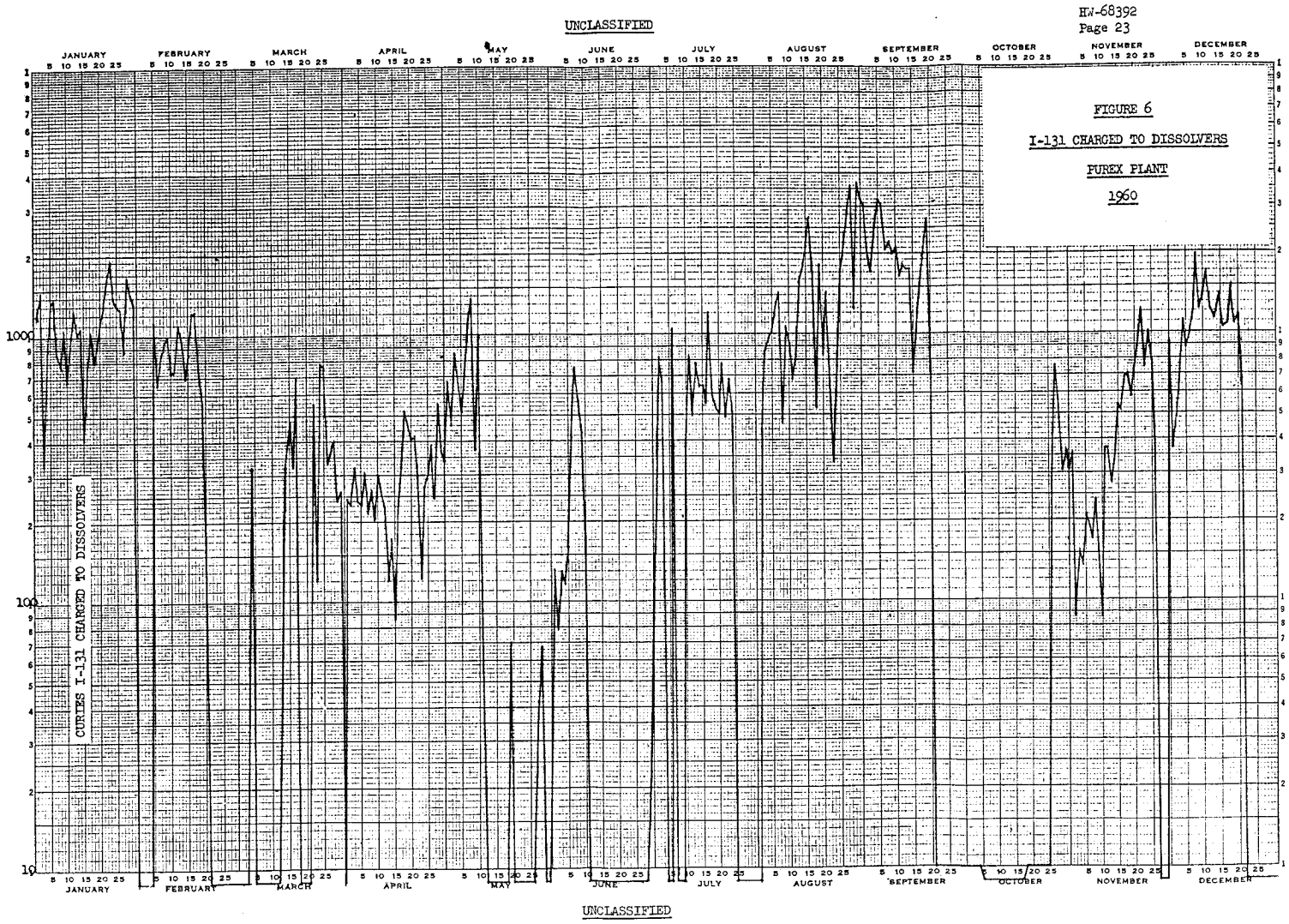


Figure 3-3. Dissolver Charging Record for PUREX 1960 (Warren 1961)

indicate that a period of considerable dissolving activity in August and September was followed by a period of no operations from about September 20 through October 26, 1960. If Heeb's accounting model were off by as little as 5 days during this period, the release ratios for September and October of 1960 could be resolved. The exact dates of releases are difficult to track; the Hanford monthly monitoring reports are not for the exact days of the reported month. The reports generally lag the actual month by about a week (i.e., the May 1959 monthly report [HW-60505] is actually for April 26 to May 24, 1959). Even this level of detail is available for very few months.

Note that Heeb describes an uncertainty factor for I-131 releases of 4.8. Applied to his calculated total values, this effectively bounds the releases reported in other contemporaneous reports.

A final method of checking the reasonableness of both Heeb's and Warren's total release estimates is to compare environmental concentrations predicted using them with the actual measurements made in the environment in 1959 and 1960 (Junkins et al. 1960; Foster and Nelson 1961). Table 3-3 illustrates the results of using an atmospheric dispersion factor estimated with the results of the HEDR atmospheric transport model RATCHET (Ramsdell et al. 1994) in conjunction with the Heeb and Warren reported total iodine releases. After the dissipation of bomb-test fallout in early 1959, it is apparent that the HEDR model would overpredict concentrations of I-131 in North Richland (HEDR node 469) by about a factor of 2 for either Heeb's or Warren's estimates of release. For neither source is the predicted environmental concentration dramatically different from the available historical evidence.

The resources are not available to completely recheck Heeb's model of radioiodine generation, throughput, and release. However, the overall HEDR estimates of I-131 release to the environment are consistent with a number of reports contemporaneous to Warren's. An increase in the variability of the releases based on monthly average cooling times rather than daily information is apparent. While the plant-by-plant releases (REDOX and PUREX) show variability, the total releases, particularly when annualized, are very similar to existing historical documentation. The apparent lack of correspondence between Warren's (1961) reported releases and the estimates of Heeb (1994) should not result in significant changes to the ultimate dose estimates calculated from the Heeb source term. Even with the apparent discrepancies between Warren and Heeb, nothing could be done, at this time, to improve the estimates of Heeb (1994).

Table 3-3. Atmospheric Concentrations of ^{131}I in North Richland Estimated Using Heeb's and Warren's Data Compared with Measurements

Year	Month	RATCHET dispersion (s/m3)	PNWD2222 Totals Ci/month	Warren Total Ci/month	Heeb Predicted (pCi/m3)	Warren Predicted (pCi/m3)	N.Richland Measured (pCi/m3)	Heeb P/O	Warren P/O	Comments
										1959 Air Data from HW-64371
1959	Jan	1.27E-08	24.63	19.13	0.117	0.091	0.332	0.352	0.273	High fallout
1959	Feb	1.26E-08	12.63	15.20	0.066	0.079	0.152	0.431	0.519	Medium fallout
1959	Mar	1E-08	19.00	12.26	0.071	0.046	0.059	1.203	0.776	Low fallout
1959	Apr	6.56E-09	13.50	33.24	0.034	0.084	0.064	0.534	1.314	Fallout free below
1959	May	6.68E-09	19.26	31.01	0.048	0.077	0.031	1.549	2.494	
1959	Jun	3.36E-09	34.02	28.64	0.044	0.037	0.015	2.937	2.473	
1959	Jul	4.2E-09	9.75	16.00	0.015	0.025	0.074	0.206	0.339	
1959	Aug	5.85E-09	32.00	29.11	0.070	0.064	0.042	1.665	1.514	
1959	Sep	7.46E-09	48.14	27.90	0.138	0.080	0.028	4.945	2.866	
1959	Oct	8.39E-09	25.46	18.02	0.080	0.056	0.055	1.449	1.026	
1959	Nov	9.64E-09	19.54	30.35	0.073	0.113	0.078	0.931	1.447	
1959	Dec	1.28E-08	27.25	36.32	0.130	0.173	0.059	1.350	1.253	
Annual total 1959			285.17	297.18			Average	1.463	1.358	1960 Air Data from HW-68435
1960	Jan	1.27E-08	94.78	24.95	0.449	0.118	0.139	3.231	0.850	
1960	Feb	1.26E-08	27.18	20.79	0.141	0.108	0.034	4.150	3.174	
1960	Mar	1E-08	4.14	13.17	0.015	0.049	0.021	0.737	2.341	
1960	Apr	6.56E-09	11.93	20.53	0.030	0.052	0.093	0.324	0.558	
1960	May	6.68E-09	12.76	16.80	0.032	0.042	0.011	2.894	3.809	
1960	Jun	3.36E-09	3.57	10.70	0.005	0.014	0.016	0.289	0.866	
1960	Jul	4.2E-09	16.64	82.77	0.026	0.130	0.015	1.738	8.642	
1960	Aug	5.85E-09	67.34	52.44	0.147	0.115	0.027	5.450	4.244	
1960	Sep	7.46E-09	5.21	53.13	0.015	0.153	0.051	0.294	2.996	
1960	Oct	8.39E-09	0.02	6.47	0.000	0.020	0.029	0.002	0.699	
1960	Nov	9.64E-09	14.00	23.41	0.052	0.087	0.011	4.733	7.914	
1960	Dec	1.28E-08	37.25	39.03	0.178	0.186	0.023	7.724	8.093	
Annual total 1960			294.84	364.19			Average	2.630	3.682	

Daily records for the periods of interest simply do not exist. Fine-tuning the Heeb estimates for 1959 and 1960 would not in any way alter or improve the estimates for 1944-1957. Furthermore, Heeb's total releases are within 15% of Warren's for the years 1959 and 1960 and the Warren estimates are well within uncertainty estimates of Heeb.

3.3 Releases throughout the 1950s and 1960s

Similar comparisons to monitored releases can be made for other years beyond 1959 and 1960. Atmospheric emissions were not continuously monitored during the early years of Hanford Site operation. Primitive equipment was installed during canyon building construction, but it was not routinely used (Patterson 1948). In addition, actual monitoring of the emissions of ^{131}I was difficult and the accuracy claimed generally ranged from a factor of 2 to 3 up to an order of magnitude. The techniques and equipment improved with time, so that by the period evaluated by Warren (1961), the accuracy should have been less than a factor of 2. It should have remained this good throughout the remainder of the operations. Routine reporting of the emissions from the T Plant stack in the Hanford Operations monthly reports begins in about March of 1951 (HW-20671). Similar routine reporting from the 200-East Area B Plant stack begins in September 1951, where in comparing T Plant and B Plant releases it is noted that "Similar monitoring facilities were established at the 200 East Area during the month" (HW-22304).

Figure 3-4 illustrates the total releases reported by month in the Hanford Health Instruments Section (later Radiological Sciences Department, Radiation Protection Operation, or Regional Monitoring Activities) sections of the Hanford Laboratories monthly reports. The full set of these reports is available through the DOE Reading Room at the Consolidated Information Center (Washington State University Tri-Cities Library). They are compared with the HEDR estimates. The values quoted here for Heeb (1994) are those revised using the mean release factor, rather than the median as originally reported. Several interesting things can be observed in Figure 3-4. First, although the question was raised about the *low* values in Heeb for REDOX in 1959 and 1960, for the year 1958 the Heeb monthly REDOX values are actually *larger* than those reported by other authors. Note the relatively high values for PUREX reported in the monthly reports for November 1958 – this is described as resulting when "…several buckets of 20 to 40 day metal were inadvertently charged and dissolved." This is the sort of thing that is not caught by Heeb's mass balance model.

Investigation of the figure illustrates that Heeb's results during the period 1959-1960 closely match the monitored data – better than any other time period. Heeb's estimates are somewhat higher in the early 1950s than the reported values. This is reasonable, because the monitoring data were not considered to be particularly accurate before and during this period. After about 1960, the releases are quite small, and even large percentage differences in release estimate are small in terms of absolute quantity.

Just as the 1959 – 1960 concentrations of ^{131}I predicted in air can be compared to the monitoring data, so can those for later time periods. Such a comparison for the period 1959-1969 is presented in Figure 3-5. Just as the monitoring data indicate, the Warren and Heeb data provide predictions of air concentration that are very similar to the measurements in the late 1950s and early 1960s, but Heeb's estimates deviate after about 1962. After this time, the releases are very low (generally less than one curie/month), and Heeb's estimates using the fuel model are about

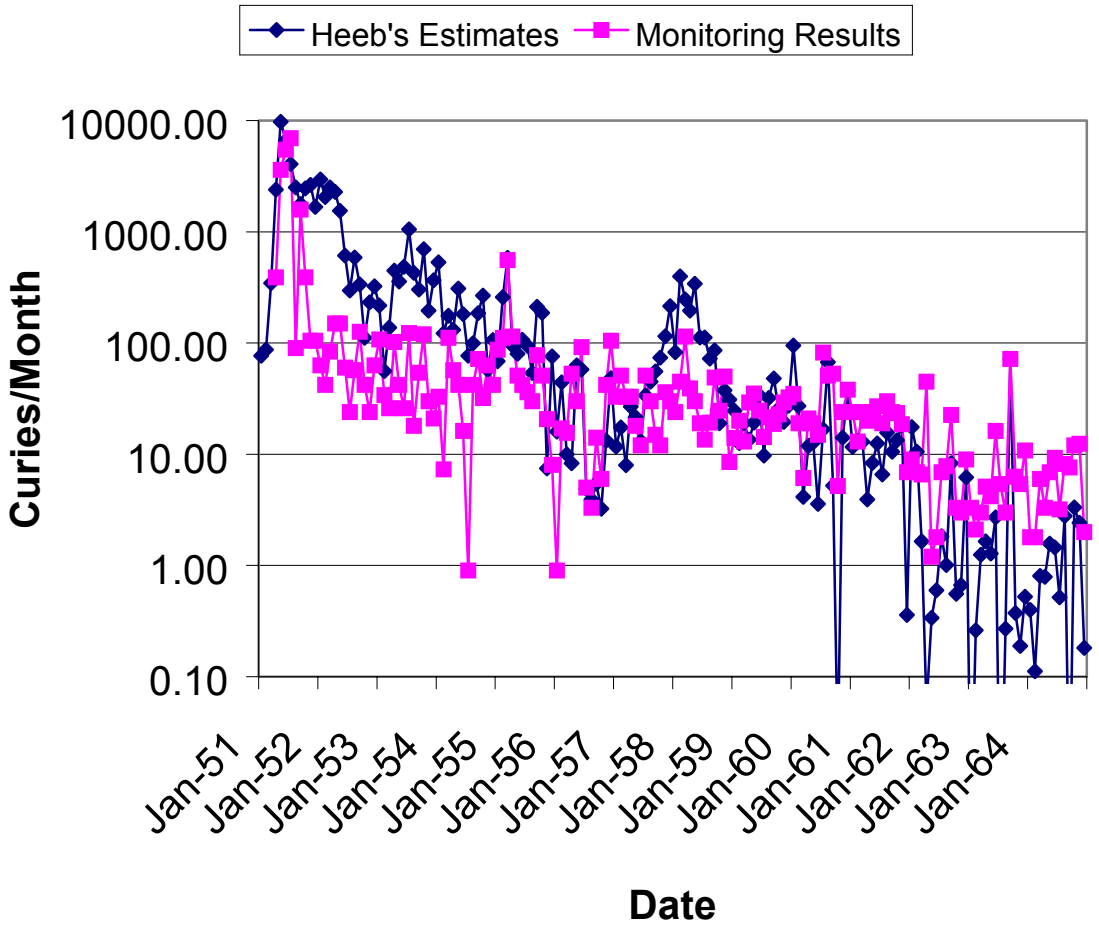


Figure 3-4. Comparison of HEDR Source Term to Monitoring Data 1951-1964.

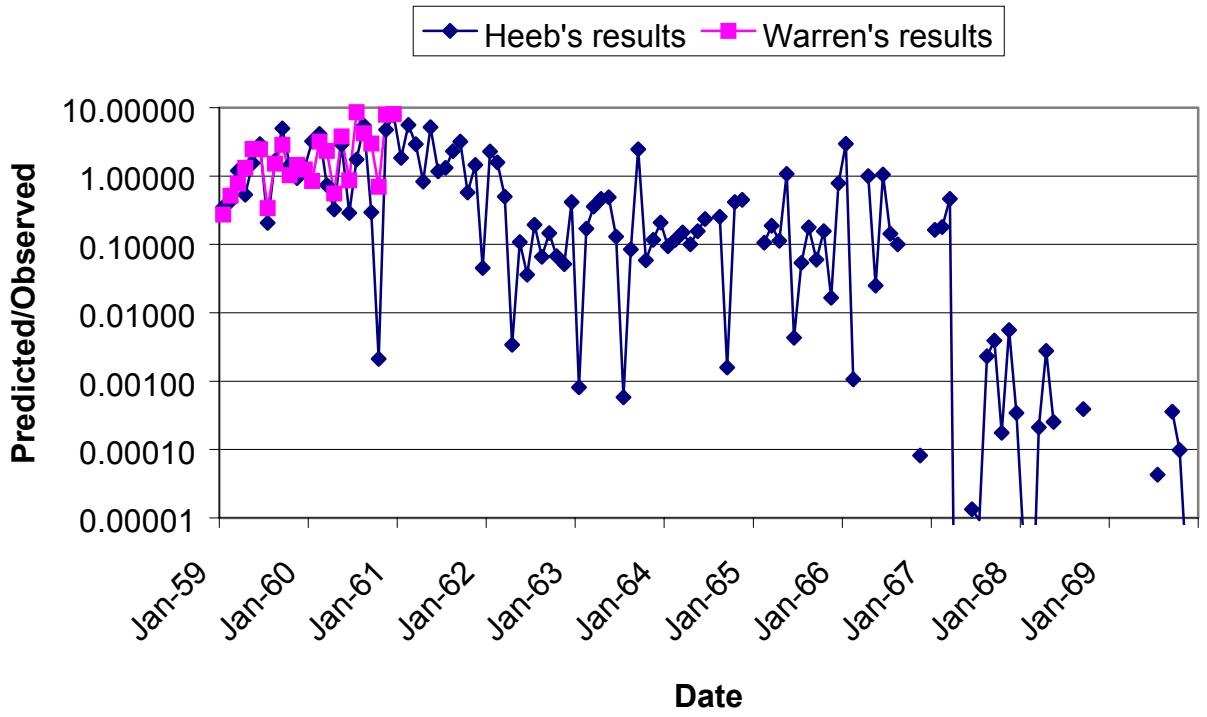


Figure 3-5. Comparison of concentrations of ^{131}I in air in North Richland predicted from release estimates to those measured, 1959 – 1970.

one-third to one-tenth what is indicated from the air measurements. The correspondence is even worse after about 1967 – but after this time, the releases are all small fractions of a curie per month, and the atmospheric monitoring results are at or below the limits of detection.

During the final decade of dissolver operations, the operators had the routine release of iodine relatively well under control. It is likely that after about 1962, the releases were dominated by unique events and abnormal operations. Therefore, Heeb's model will only reliably report a fraction of the total release after that time. This is a likely interpretation of the latter portion of the curves in Figure 3-5. What this implies is that *no* model is likely to succeed in simulating the releases in the late 1960s – they are best estimated using the stack monitoring data, with some minor adjustment to account for the inaccuracies of those systems. However, the total release estimated by Heeb after 1962 until the cessation of fuel processing in 1972 is less than 150 curies in total – less in 10 years than in any one month in 1945 through mid-1948.

3.4 Propagation of source term uncertainty

The National Academy of Sciences (NAS 1999) review of the HEDR dosimetric methods presents several assertions of underestimation of release based on an analysis by Hoffman et al (1999). One of the assertions is that "the HEDR project did not propagate the source-term uncertainties into air concentrations, ground deposition, and doses."

The HEDR project team developed the RATCHET (Ramsdell et al. 1994) and DESCARTES (Nichols et al. 1994) computer codes to evaluate the environmental concentrations of ^{131}I from the source terms developed by Heeb (Heeb 1993, 1994). The source terms from the time period of greatest interest were developed for the T and B Plants on the basis of detailed information, and were presented hourly. The uncertainties in the releases were developed using Monte Carlo methods. Hourly meteorological data were used to estimate the atmospheric dispersion and deposition; uncertainties in the dispersion and deposition were addressed through minor variabilities in the atmospheric data, but the primary source of uncertainty in the predicted concentrations was actually the timing of the releases (generally within a few dozen hours).

However, for the time period beginning in 1950, the detailed information that allowed hourly source term reconstruction was not available. In addition, the hourly meteorological data for the Hanford Meteorological Station was also not found for the period beginning in 1950 through 1951. Therefore, two approximations had to be made, one for the source and one for the dispersion. These are described in some detail in Shipler and Napier (1994).

For the source terms, monthly estimates were developed (Heeb 1994). These were based on more general records of fuel burnup, throughput, and cooling. The batch-by-batch details that allowed the hourly estimation were not available. Thus, it was not possible to calculate the most important input in terms of dispersion and deposition – the timing of the release with respect to the wind direction.

Because neither the source term nor the meteorological data supported the hourly dispersion information from 1950 through 1951, the HEDR team decided to use surrogate information. The detailed modeling of the period December 1944 through December 1949 had provided series of 100 realizations of air concentration and deposition by day for each month. The realizations for the year 1945 were excluded, because the release histories were quite erratic at the beginning of the operation. Thus, there was a minimum of 400 realizations available for each

month. It is important to realize that a single realization includes the complete daily history for the entire month. Each of these realizations includes information on release rates, wind speeds and directions, and precipitation for an entire month. When the numerical values of air concentration and deposition rate in these realizations are divided by the appropriate monthly release rate, the result is an effective normalized dispersion factor for the month. This set of normalized dispersion factors inherently includes all uncertainties in release timing, wind speed and direction, precipitation, and plume depletion. A randomly selected set of 100 of these realizations for each month was used in the calculations for the years after 1949.

The monthly realizations from 1946 through 1949 were divided by the mean of the release rate for those months. Therefore, the mean monthly releases reported in Heeb could be used directly as inputs for the later years. Hoffman's observation is correct that the uncertainties directly associated with the later years' releases could not be directly input using this system. It was not possible to deconvolute the uncertainties in 1946 through1949 source terms from the normalized dispersion factors. Although the uncertainties in the later years monthly releases are higher than the earlier ones (a 95% confidence level factor of 4.8 [Heeb 1994 page 4.17] versus an earlier coefficient of variation of only about 10%), this was accepted by the HEDR team. The uncertainties in the dispersion factor include the smaller coefficient of variation. The uncertainties in dispersion added by the lack of knowledge of the timing of the releases have a much larger effect than the uncertainties in the release amount, and the omission of the source term uncertainty is negligible.

The HEDR intermediate data file that contains the air concentrations and depositions input to the DESCARTES code was queried. Figure 3-6 illustrates the distribution in daily estimated concentration of ^{131}I in air in Pasco and Kennewick, Washington (a nearby node) for 1948. This set of realizations uses the full suite of information available on release rates, release times, hourly meteorology, and their associated uncertainty. Figure 3-7 illustrates the distribution in daily estimated concentrations of ^{131}I in air in Pasco and Kennewick for 1954. This set of realizations uses the mean release from Heeb (1994), and the surrogate release rates, release times, and hourly meteorology. The years 1948 and 1954 were selected for this comparison because they have releases of similar magnitude. Notice that the estimated air concentrations on any particular day span many orders of magnitude. In this figure, values less than 10^{-16} have been suppressed - which include numerous realizations of zero.

The air concentrations illustrated in Figure 3-7 have an unusual distribution for any day, with results spanning over 6 orders of magnitude. The distributions estimated using the surrogate data are similar in magnitude to those calculated using detailed data, however, there are some differences. The surrogate data have fewer zero days; the wind blows towards the location in some realizations and away from it in others. Some days may have multi-modal distributions, see for instance Figure 3-8, which compares the distributions for Day 70 (March 10 or 11, depending on leap years) of years 1948, 1951, and 1954. Notice that the detailed 1948 data indicates about a 40 percent probability of zero air concentration on this day. Notice, too, that the 1951 and 1954 results are similar to each other, differing mostly in magnitude, because both were drawn from the same set of surrogate data. Because this surrogate data includes results from 1948 as well as other years with lower probabilities of zero concentration, there is a lower chance of zero. The 1951 and 1954 results appear to have been selected from at least a high-dispersion and a low-dispersion set of possibilities, as well as a chance of zero.

Removing the small uncertainty of the 1940s source term and adding the uncertainty of the later years' source term, a lognormal distribution with a geometric standard deviation of about 2.2 (Heeb 1994), would have a very small impact on these distributions. Such an addition would be centered on the release rates used and would not shift the mean of the resulting distributions, nor noticeably effect the extremes of the distributions, as can be demonstrated with simple examples in the Excel spreadsheet add-in Crystal Ball™.

We acknowledge that the HEDR team did not do a good job of explaining and characterizing the uncertainty distribution resulting from the surrogation process used. However, it is plain from the HEDR intermediate data that this process was a success. The overall uncertainty in the daily ^{131}I environmental concentrations is quite large and encompasses any omitted uncertainty in the stack releases. We continue to believe that there is no more appropriate method available for the 1950s.

Figure 3-6. Distributions of daily estimated air concentrations at HEDR Node 443 (Pasco and Kennewick, Washington) for the year 1948.

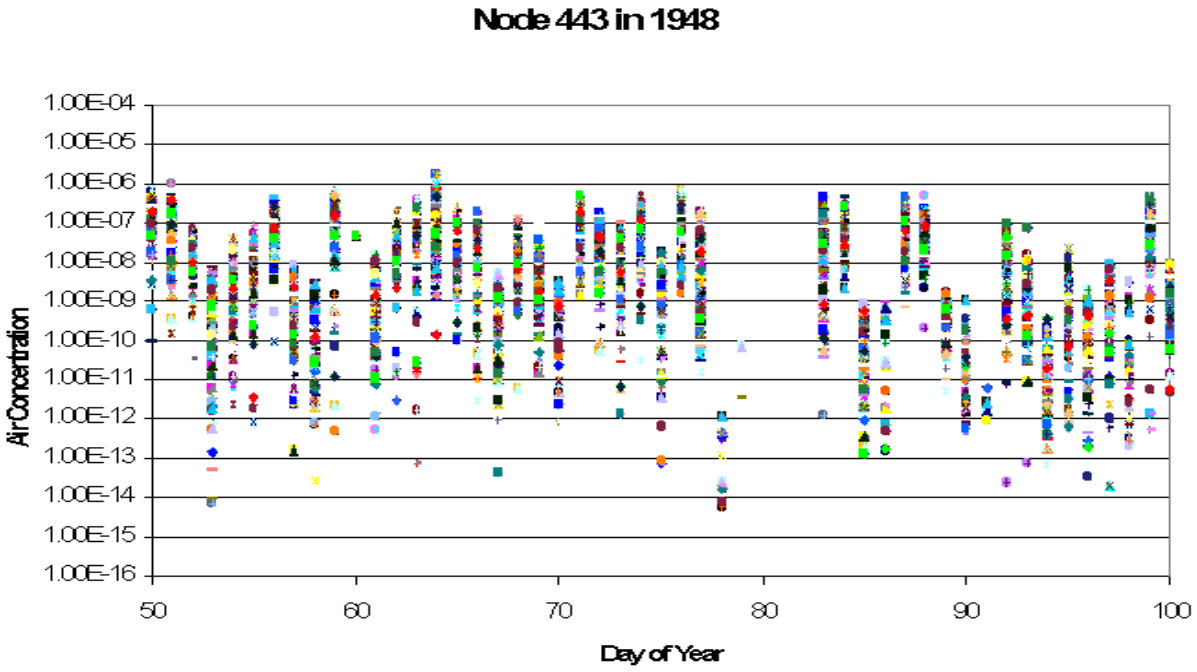


Figure 3-7. Distributions of daily estimated air concentrations at HEDR Node 443 (Pasco and Kennewick, Washington) for the year 1954.

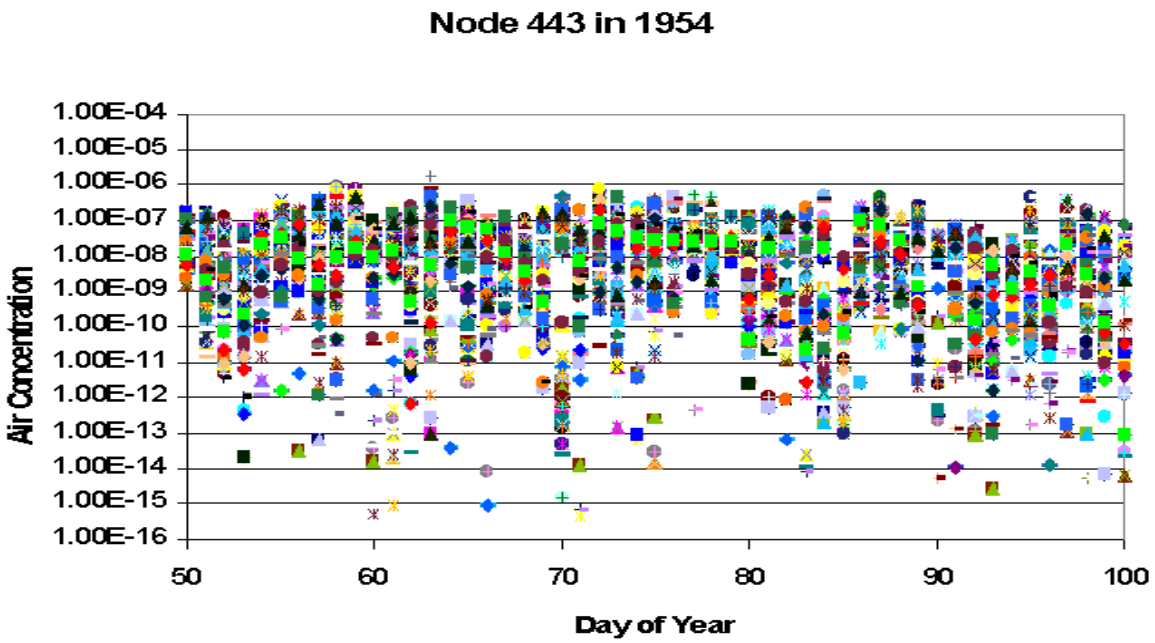
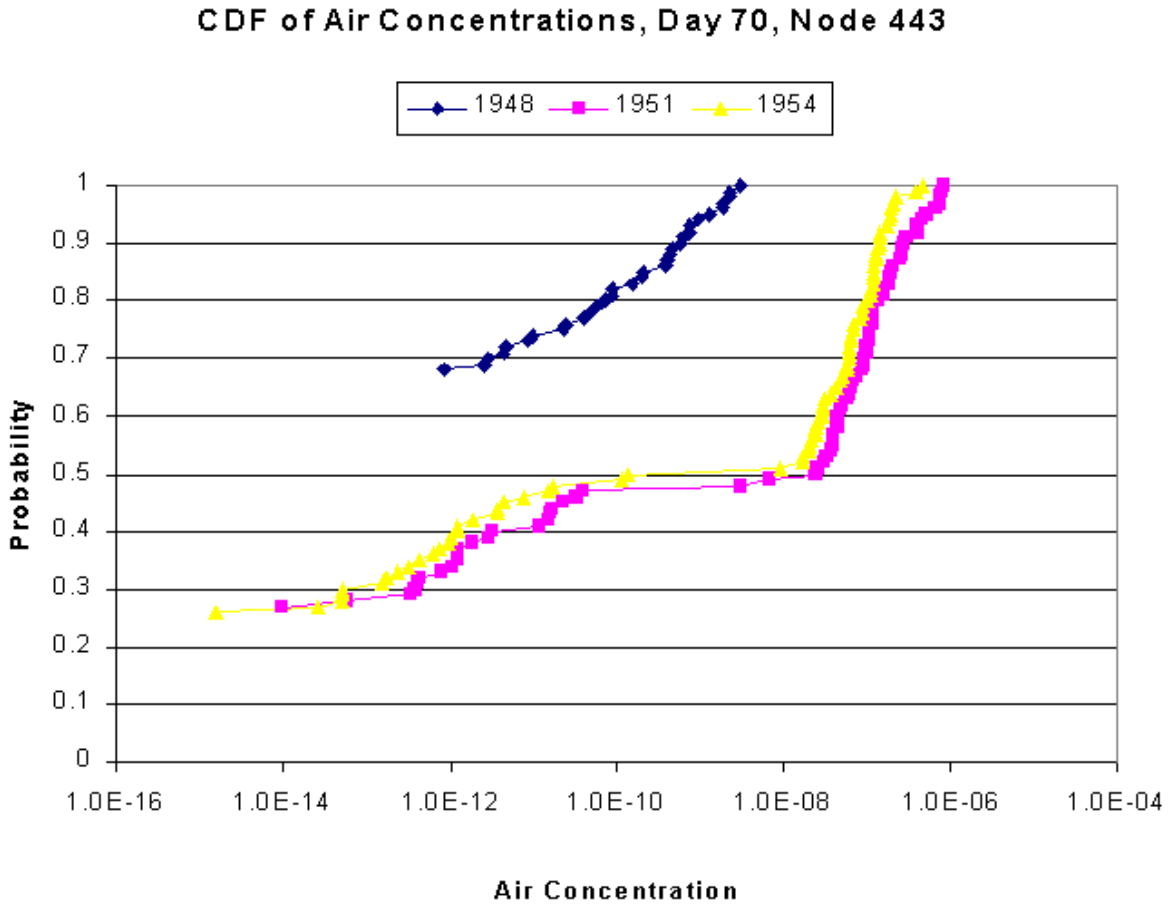


Figure 3-8. Cumulative distribution functions of estimated air concentration for HEDR Node 443 (Pasco and Kennewick) for Day 70 of three separate years.



3.5 Summary of Source Term Model Assessment

The HEDR source term was developed using a data-intensive, but relatively simple, model. As has been noted, "All models are wrong; some models are useful" (Box 1979). It is easy to disparage models piece by piece when they are assessed in a vacuum of information. However, the HEDR model is based on an enormous amount of well-defined data. In addition, it was not developed in a vacuum, either – many of the parameter selections were made with knowledge of the overall system in such a way as to reproduce that system. Individual components of the model were extensively reviewed internally, by the Technical Steering Panel, and externally.

Statistically, representing the releases using either the mean or the median of the distribution is valid; however, because the results were described as being means while actually being medians, they were used as means. The resulting initial calculations of intake for the effected time periods were therefore in error. This problem has been corrected, and all subsequent calculations use the correct inputs.

There is a large database of corroborating information. This includes historical stack monitoring and environmental samples. The collective assembly of information indicates that the HEDR model is robust, reasonably accurate, and well-suited for its task. According to some of this historical information, the HEDR model may break down in the mid- to late 1960s. However, the releases in this last period are very small.

We acknowledge that the HEDR team did not do a good job of explaining and characterizing the uncertainty distribution of the atmospheric concentration and deposition data resulting from the release-and-dispersion surrogation process used. However, it is plain from the HEDR intermediate data that this process was a success. The overall uncertainty in the daily ^{131}I environmental concentrations is quite large and encompasses any omitted uncertainty in the stack releases.

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4. Farm Animal Feeding Regimes Used in HEDR

Output from the soil and vegetation submodel of the HEDR code DESCARTES provides the concentration of radionuclides in environmental media (soil and vegetation) at each grid node. Dairy cows and other animals are assumed to have eaten several types of diets, with a diet defined as a sum of fractional feed-type intakes. The amount of each feed type eaten by the various animals may be graphically represented as in Figure 4-1 (Beck et al. 1992). Four feeding regimes for dairy cattle were initially anticipated to be provided by the Demography, Food Consumption, and Agriculture Task: two diets related to irrigated farms and two to non-irrigated farms (Beck et al. 1992). However, the Technical Steering Panel became involved late in the project and required more feeding regimes; four for backyard (family or small farm) cows and four for commercial diaries. Milk provided by any combination of these types of cows was allowed to be combined into creamery- and grocery-supplied milk.

The use of fractional intakes of various types of feed introduces a minor complication within the animal feeding model. Each of these fractions has its own distribution. The results of the selection process of the fractions must, however, sum to 1.0, which implies a correlation structure. The means of handling this potential correlation is a simple adjustment rule because there is no strong information on possible correlations. The various fractions were drawn independently from their distributions, and the sum of the results was used to normalize each value so that the total then added to 1.0.

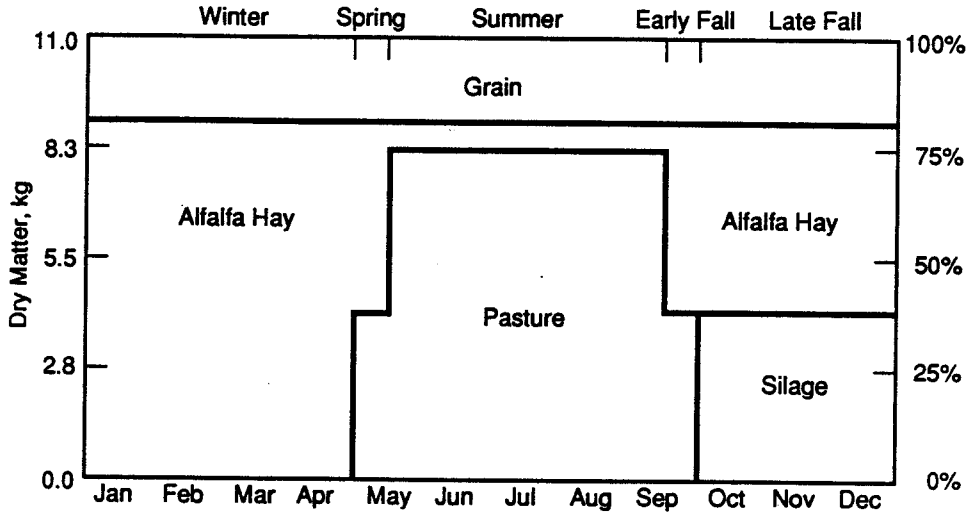

Figure 4-1. Typical cow feeding regime (Beck et al. 1992)

The quantity of a radionuclide consumed by an animal at a given location on a given day can be expressed as (Ikenberry et al. 1993)

$$A_{cons}(d,l) = \sum_{k=1}^{L} \sum_{t=1}^{T} f_{kt}^{dl} \, QF_t^{dl} \, C_{kt} \, e^{-\lambda_r (d - j_{kt})}$$

where $A_{cons}(d,l)$ = radionuclide consumption rate of the animal at location l on day d, Ci/d

d = current day

l = current location (where feed was eaten by animal)

L = total number of potential feed source locations

T = total number of feed types

j_{kt} = Julian day on which feed t was harvested at location k

k = location where feed was grown and harvested

f(d,l,k,t) = fraction of feed type t eaten by the animal at location l during day d that was harvested at location k (from feed source/transport matrix). The sum of these fractions over all k for a given feed type, t, for the current location, l, and day d must equal 1.0.

QF(d,l,t) = quantity of feed of type t that the animal at location l eats during day d (kg/d dry weight). This is from the data on feeding regimes (Beck et al. 1990).

C(k,t) = radionuclide concentration (Ci/kg) in feed of type t harvested on day j at location k from soil and vegetation model

λ_{rad} = radioactive decay constant for nuclide r (d^{-1})

$(d-j_{kt})$ = decay correction time for feeds not consumed fresh (d).

The term f(d,l,k,t) is a complex matrix defining what feeds were provided to animals at what times. The definitions of feed include the dates at which they were harvested or at which animals were put on to pasture. (Thus, there may be several cuttings of alfalfa, each considered to be a different "type" of feed.) The individual parameters defined above vary over time and space. The combination of amount of feed, its production history, and the dates at which the quantities and/or types change is called an animal's feeding regime.

4.1 Dairy Cattle Feeding Regimes

The feeding regimes used for cows in the HEDR representative dose calculations, and transferred to HTDS for use in the epidemiology, are fully documented by TSP member Dr. David Price (Price 1994). A copy of his report has been provided to the HTDS team. Dr. Price worked with staff of the HEDR Demography, Food Consumption, and Agriculture Task to establish the diets. He personally performed a small survey of 9 farmers from the 1940s. His information was combined with that of other sources such as the Washington Dairy Herd Improvement Association to establish the four feeding regimes for backyard (family or small farm) cows and four for commercial diaries. Sensitivity studies by Napier (1994) indicated that minor differences beyond these four major regimes did not have noticeable impact on the overall estimated milk concentrations.

In the HEDR scheme, five seasons are required to define a feeding year. The first season starts on January 1 and the last ends on December 31. The seasons are winter, spring, summer, early fall, and late fall. The start and stop times of the seasons are controlled by what are called "frost date files" in the HEDR system. The frost date files were designed to control the growing season of pasture grass and other vegetation, and were adapted, in separate runs, to control the feeding regimes as specified by Dr. Price.

Types of feed available for cows to eat in the HEDR codes included fresh pasture, grass hay, alfalfa hay, grain, silage and/or green chop. In the HEDR system, hay could be harvested several times per year, depending on location and farming practice. Additional secondary pathways of exposure to cattle included intake from deposition on stored feeds (termed "manger" intake in the codes), intake from deposition on stock water tanks, and incidental intake from soils.

The following paragraphs are adapted from Dr. Price's report. The tables from his report are duplicated here for those who may not have access to an original copy of his report.

The HEDR dose model requires that uncertainties be specified for each variable input. This first requires that specific distribution be selected. For dry matter intakes, distributions with infinite tails such as the normal distribution were deemed non-applicable. Two distributions with finite tails were considered; the uniform and the triangular. The

triangular distribution was selected since it allows probabilities to decrease as values change from an "average". The HEDR code allows the triangular distribution to be non-symmetric. Therefore, this feature was used where appropriate. This also means that the "average" value is the mode.

The first regime for the family cow had no pasture. Since total dry matter intake is less when cows are not on pasture its mode was specified to be 9.6 kilograms throughout the year with range of 7.6 to 11.6 kilograms. Hay was specified to contribute 8.1 kilograms while grain contributed 1.5 kilograms. The range on hay was specified to vary between 7.1 and 9.1 kilograms, while that for grain was from 0.5 to 2.5 kilograms. This regime is identified in the HEDR files as BY4 (back-yard type 4).

No family cow regime contained any silage or green chop. Silage requires an appropriate, nearly air tight storage facility. None of the nine farmers interviewed fed silage or green chop. Furthermore, in 1945 it was relatively expensive to build such a facility. Machinery for green chopping was not on the market in 1945. However, hand scythes and hand corn cutters were available.

The pasture on and off dates, the seasons which meet code requirements, and the dry matter intake for family cows on irrigated pasture are shown in Table 4-1. This is HEDR type BY1. For each area there is a 15-day period where the cows adjust to being on pasture. The same adjustment period is used at the end of the pasture season. During the full pasture season, 90 percent of the dry matter intake stemmed from pasture. This was the same percentage that the experts specified for the peak non-irrigated pasture.

Even though feeding regimes are important to dose, scoping studies using the Battelle model have shown that the uncertainties associated with feeding regimes are a minor factor in the total uncertainty associated with dose. In that model, wide uncertainties have been attached to the feed-to-milk transfer factor and to the transfer factor that relates human milk consumption to thyroid dose. The uncertainties for pasture seasons (shown in parentheses, Table 4-1) were based on those expressed by the experts with slight modifications made by Dr. Price. The uncertainties allow for the possibility that nearly all dry-matter intake comes from pasture.

The feeding regimes meeting the code requirements for family cows on non-irrigated grass pasture followed by wheat stubble are given in Table 4-2. This represents both HEDR types BY2 and C1 (commercial type 1). The total dry matter intakes were allowed to decline as the pasture season progressed. This decline specified the effect of the deterioration in non-irrigated pasture over the season. In addition to the decline in total dry matter intake, the amount of hay fed was increased as pastures deteriorated. The decline in the percent of dry matter intake from pasture was specified to be in agreement with the opinions of the experts. The percent of dry matter from pasture varied from 75 percent in the first two months of the pasture season to about 32 percent in the last two months.

The pasture on and off dates were those given by the three experts. The uncertainties allowed the percent of dry matter from pasture to be as high at 84 percent in the first two months of the pasture season to as low as about 15 percent in the last two months. The uncertainties allowed the possibility of no grain being fed during the pasture season.

The feeding regimes for family cows on non-irrigated pasture with no wheat or stubble pasture are specified in Table 4-3. This is HEDR type BY3. The dates cows were taken off pasture represent a combination of the opinions of the three experts. The dates on pasture were those specified by the experts

The non-irrigated pasture regimes with no wheat or stubble were similar to those with stubble. The major differences were an earlier off date and less dry matter intake from pasture during the latter part of the pasture season.

Pasture on and off dates for commercial dairies with cows on irrigated pasture (Table 4-4, HEDR type C2) were identical to those for the family cow. The dry matter intakes for the commercial operations were higher as estimated in the previous section. Unlike the family cow, some hay was fed while cows were on full pasture. The amount of dry matter from pasture was specified to be consistent with expert opinion. That is, the percent of dry matter from irrigated pasture was specified to be 75 percent, the same as the percentage from peak non-irrigated pasture.

Silage was included in the commercial irrigated regimes during the autumn months. No silage was specified for other seasons. Due to storage time, its contribution to dose in other seasons would be negligible.

The commercial feeding regimes with non-irrigated pastures did not include silage (Table 4-5, HEDR type C3, and Table 4-6, HEDR type C4). In the HEDR area, it is not feasible to raise corn without irrigation. Feeding of grass silage was limited during the 1945-1951 period.

The two commercial feeding regimes for non-irrigated pasture use the same pasture on and off dates and seasons as these regimes for the family cow. The percentage of dry matter intake from pasture is the same as the commercial irrigated regime for the peak pasture season. The percentages then decline over the season as specified by the experts. Hay is used to supplement pasture and grain throughout the pasture season.

For non-irrigated pasture with stubble, 43 percent of the dry matter intake came from pasture. This is the same percentage as that for non-irrigated pasture without stubble. This contrasts with 74 percent for irrigated pasture.

Under irrigated family cow regimes, the percent of dry matter intake from the various pasture regimes over the entire year for the various areas range from 38 to 53 percent. With the uncertainties, this figure can range between 28 to 63 percent. The between area differences are the result of the longer pasture seasons in the warmer areas of the HEDR domain.

The percent dry matter for the non-irrigated pastures is quite constant across areas. Pasture season begins earlier in the warmer areas, but it also ends at an earlier date. In addition, pasture quality declines more rapidly over the year. The ranges in dry matter intake within a given geographic area are wider for non-irrigated pasture than for irrigated pasture. This depicts the wide variation both in size of pasture and in moisture conditions that exist within a given geographic area.

The percent dry matter intakes from pasture for the commercial operations are all lower than those for the family cow. The differences between areas and within areas are similar to those for the family cow.

4.2 Feeding Regimes for Other Farm Animals

Other farm animals for which concentrations of ^{131}I were calculated in the DESCARTES code are beef cattle (for meat), chickens (for meat and eggs), and goats (for milk). It appears that the HEDR feeding regimes for these animals have never been formally published. Therefore, the original data input files for the DESCARTES calculations used by the CIDER code were recovered, and the contents put in a form parallel to the tables generated by Dr. Price. Significantly less effort went into the generation of these input selections, and there is only a single variant for each animal. However, the season lengths for each animal are tied to the same regions as the dairy cattle, and thus there are regional variations in the feeding regimes that vary through the year.

Table 4-7 presents the basic feeding regime for beef cattle. As with the dairy cattle, the ranges for each feed type are uniform and constrained to a range of maximum values. Intakes of hay are further broken down into alfalfa hay and grass hay. Grass hay was an option available for all feeding regimes; however, it was not selected by Dr. Price for any of the back yard or commercial dairy cow feeding regimes. Hay in all of the dairy cattle feeding regime tables refers to alfalfa hay. Not shown in the table are additional small intakes via drinking water from stock tanks, consumption of dirt along with the feed, and fallout onto the manger.

Table 4-8 presents the basic feeding regime for poultry. Laying hens and frying hens are assumed to eat the same diet. As with the dairy cattle, the ranges for each feed type are uniform and constrained to a range of maximum values. Not shown in the table are additional small intakes via drinking water from stock tanks, and consumption of dirt along with the feed.

Table 4-9 presents the basic feeding regime for dairy goats. Unlike with the other animal types, only the ranges for the pasture feed type are uniform, the others are assigned a triangular distribution as indicated. All intakes are constrained to a range of maximum values. Not shown in the table are additional small intakes via drinking water from stock tanks, and consumption of dirt along with the feed.

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Table 4-1 : Feeding Regimes for Family Cows; Irrigated Pasture

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	90 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/1 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	184 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	138 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

III. Areas: Colville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/5 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	133 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	123 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	10/1 (+-15)	92 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	110 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/20 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	153 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	10/20 (+-15)	72 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	153 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	169 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/10 (+-15)	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
C	B+15 days	174 (+-30)	9.9 (+-1)	0	1.1 (+-1)	11.0 (+-2)
D	E-15 days	15	6.6 (+-2)	3.3 (+-2)	1.1 (+-1)	11.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

Table 4-2 : Feeding Regimes for Family Cows; Nonirrigated Pasture, with Stubble.

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	90 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	92 (+-30)	5.57 (-2.4+3.2)	3.93 (-2.4+3.2)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.25 (-2+3.5)	5.35 (-2+3.5)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	62 (+-30)	6.32 (-2+3)	3.18 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.74 (-2+3)	4.86 (-2+3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

III. Areas: Collville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/5 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	57 (+-30)	6.4 (-2+3)	3.1 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.91 (-2+3)	4.69 (-2+3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	62 (+-30)	6.3 (-2+3)	3.2 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.76 (-2+3)	4.84 (-2+3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	110 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/20 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	72 (+-30)	6.0 (-2.3+3.1)	3.5 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.58 (-2+3.1)	5.02 (-2+3.1)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	77 (+-30)	5.87 (-2.3+3.1)	3.63 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.5 (-2+3.3)	5.1 (-2+3.3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	77 (+-30)	5.87 (-2.3+3.1)	3.63 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.5 (-2+3.2)	5.1 (-2+3.2)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/10 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	82 (+-30)	5.76 (-2.3+3.1)	3.74 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.4 (-2+3.3)	5.2 (-2+3.3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

Table 4-3: Feeding Regimes for Family Cows; Nonirrigated Pasture, No Wheat or Stubble.

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	90 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	61 (+-30)	6.35 (-2+3)	3.15 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	1.9 (-1.9+3.5)	6.7 (-1.9+3.5)	1.0 (+-1)	9.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	31 (+-30)	7.4 (-2+2.4)	2.1 (-2+2.4)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	4.1 (-2+3.4)	4.5 (-2+3.4)	1.0 (+-1)	9.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

III. Areas: Colville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/5 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	31 (+-30)	7.4 (-2+2.4)	2.1 (-2+2.4)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	4.1 (-2+3.4)	4.5 (-2+3.4)	1.0 (+-1)	9.6 (+-2)
E	10/5 (+-15)	87 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	5/1 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	31 (+-30)	7.4 (-2+2.4)	2.1 (-2+2.4)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	4.1 (-2+3.4)	4.5 (-2+3.4)	1.0 (+-1)	9.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	110 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/20 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	61 (+-30)	6.35 (-2+3)	3.15 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	1.9 (-1.9+3.5)	6.7 (-1.9+3.5)	1.0 (+-1)	9.6 (+-2)
E	10/20 (+-15)	72 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	61 (+-30)	6.35 (-2+3)	3.15 (-2+3)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	1.9 (-1.9+3.5)	6.7 (-1.9+3.5)	1.0 (+-1)	9.6 (+-2)
E	10/15 (+-15)	77 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake			
			Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/15 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	77 (+-30)	5.87 (-2.3+3.1)	3.63 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.5 (-2+3.2)	5.1 (-2+3.2)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake			
			Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)
B	4/10 (+-15)	61	8.25 (+-1)	1.75 (+-1)	1.0 (+-1)	11.0 (+-2)
C	B+61 days	82 (+-30)	5.76 (-2.3+3.1)	3.74 (-2.3+3.1)	1.0 (+-1)	10.5 (+-2)
D	E-61 days	61	3.4 (-2+3.3)	5.2 (-2+3.3)	1.0 (+-1)	9.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	8.1 (+-1)	1.5 (+-1)	9.6 (+-2)

Table 4-4: Feeding Regimes for Commercial Production; Irrigated Pasture

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	90 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/1 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	184 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	138 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

III. Areas: Colville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/5 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	133 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	123 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/1 (+-15)	92 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	110 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/20 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	153 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/20 (+-15)	72 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	153 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	169 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/10 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	174 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	11/1 (+-15)	61 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

Table 4-5: Feeding Regimes for Commercial Production; Nonirrigated Pasture, No Wheat or Stubble

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season Date	Start Days	No. Pasture Days	Dry Matter Intake Season Hay	Grain	Total	
A	1/1	90 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/1 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.8 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	31 (+-30)	6.67 (-2+1.6)	4.33 (-2+1.6)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	3.0 (-1.2+3.5)	7.3 (-1.2+3.5)	1.3 (+-1)	11.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

III. Areas: Colville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/5 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	31 (+-30)	6.87 (-2+1.6)	4.33 (-2+1.6)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	3.0 (-1.2+3.5)	7.3 (-1.2+3.5)	1.3 (+-1)	11.6 (+-2)
E	10/5 (+-15)	87 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	31 (+-30)	6.87 (-2+1.6)	4.33 (-2+1.6)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	3.0 (-1.2+3.5)	7.3 (-1.2+3.5)	1.3 (+-1)	11.6 (+-2)
E	10/1 (+-15)	92 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	115 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/20 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/20 (+-15)	72 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/15 (+-15)	77 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/15 (+-15)	77 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/10 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/10 (+-15)	82 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

Table 4-6: Feeding Regimes for Commercial Production; Nonirrigated Pasture, with Stubble

I. Areas: Yakima Valley, Lewiston, Walla Walla, Umatilla, Central Basin, Ringold

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	90 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/1 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	92 (+-30)	4.73 (-2.4+2.8)	6.47 (-2.4+2.8)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	2.5 (-2+3.3)	7.8 (-2+3.3)	1.3 (+-1)	11.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

II. Areas: Spokane, Pullman

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	62 (+-30)	5.56 (-2+2.5)	5.64 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	2.75 (-2+3)	7.55 (-2+3)	1.3 (+-1)	11.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

III. Areas: Colville

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	125 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/5 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	57 (+-30)	5.69 (-2+2.4)	5.51 (-2+2.4)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	2.88 (-2+3)	7.42 (-2+3)	1.3 (+-1)	11.6 (+-2)
E	11/1 (+-15)	61 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)

IV. Areas: Okanogan

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	120 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	5/1 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	123 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/1 (+-15)	92 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

V. Areas: Wenatchee, Pomeroy, Lacrosse

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	110 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/20 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	153 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/20 (+-15)	72 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

VI. Areas: Pendleton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+15 days	153 (+-30)	9.75 (+-1)	1.95 (+-1)	1.3 (+-1)	13.0 (+-2)
D	E-15 days	15	8.45 (+-1)	3.25 (+-1)	1.3 (+-1)	13.0 (+-2)
E	10/15 (+-15)	77 (+-15)	0	4.95 (+-1)	1.7 (+-1)	11.6 (+-2)

Season E should include 4.95(+-1) of silage.

VII. Areas: Dayton

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	105 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/15 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/15 (+-15)	77 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

VIII. Areas: Kittitas Valley

Season	Start Date	No. Days	Dry Matter Intake Pasture	Hay	Grain	Total
A	1/1	100 (+-15)	0	9.9 (+-1)	1.7 (+-1)	11.6 (+-2)
B	4/10 (+-15)	61	9.1 (+-1)	2.6 (+-1)	1.3 (+-1)	13.0 (+-2)
C	B+61 days	61 (+-30)	5.62 (-2+2.5)	5.58 (-2+2.5)	1.3 (+-1)	12.5 (+-2)
D	E-61 days	61	1.17 (-1+3.5)	9.13 (-1+2.5)	1.3 (+-1)	11.6 (+-2)
E	10/10 (+-15)	82 (+-15)	0	9.90 (+-1)	1.7 (+-1)	11.6 (+-2)

Table 4-7. Feeding Regimes for Beef Cattle, Intakes in kg/day of dry matter. All distributions are uniform.

Season	Pasture	Alfalfa Hay	Grass Hay	Grain	Total
Winter	0 – 2	0 – 7.5	0 – 7.5	0 – 1.5	8.5 – 15
Spring	0.5 – 2.5	0 – 4.5	0 - 2	0 – 4.5	7.5 – 12
Summer	1 – 8	0 – 2	0	0 – 3	6.5 – 10
Early Fall	1 – 4	0 – 2	0 – 2	0 – 6	7.5 – 13
Late Fall	0 – 1.5	0 – 4.5	0 – 4.5	0 – 7	8 – 13

Table 4-8. Feeding Regimes for Poultry, Intakes in kg/day of dry matter. All distributions are uniform.

Season	Pasture	Alfalfa Hay	Grass Hay	Grain	Total
Winter	0 – 0.03	0 – 0.01	0	0.04 – 0.10	0.06 – 0.16
Spring	0.01 – 0.04	0.005 – 0.01	0	0.03 – 0.10	0.05 – 0.15
Summer	0.02 – 0.05	0.005 – 0.01	0	0.02 – 0.07	0.04 – 0.11
Early Fall	0.01 – 0.05	0.005 – 0.01	0	0.02 – 0.08	0.04 – 0.12
Late Fall	0 – 0.04	0 – 0.01	0	0.03 – 0.10	0.05 – 0.15

Table 4-9. Feeding Regimes for Dairy Goats, Intakes in kg/day of dry matter. Distributions for Pasture and Total are uniform, all others are triangular; values presented are the minimum, mode, and maximum of the distribution.

Season	Pasture	Alfalfa Hay	Grass Hay	Grain	Total
Winter	0	0.9 – 1.4 – 1.6	0	0.8 – 2 – 3.2	1.2 – 4.5
Spring	0.6 – 1.0	0.9 – 1.4 – 1.6	0	0.8 – 2 – 3.2	1.2 – 4.5
Summer	0.6 – 1.0	0.9 – 1.4 – 1.6	0	0.8 – 2 – 3.2	1.2 – 4.5
Early Fall	0.6 – 1.0	0.9 – 1.4 – 1.6	0	0.8 – 2 – 3.2	1.2 – 4.5
Late Fall	0	0.9 – 1.4 – 1.6	0	0.8 – 2 – 3.2	1.2 – 4.5

5. Feed-to-Milk Transfer

The factors relating transfer of ^{131}I from cows' feed to milk are described in Snyder et al. (1994). Based on review of historical reports, Snyder et al. defined a range for the parameter F_m, the feed-to-milk transfer coefficient for individual cows, with a median of 0.0092 day/liter and a geometric standard deviation of 2.1. The mean value of this distribution was applied to herds of cows, which is a surrogate for estimating the milk from each cow and then pooling it at a collection center. The mean value of the distribution is 0.012 day/liter.

The National Academy of Sciences review of the Hanford Thyroid Disease Study dose methodology suggests that the HEDR values "seem to be too high by a factor of about 2" compared with other values used in recent studies with which the NAS authors are familiar. They do note, however, that "this is an open issue, in that the measured values of this transfer coefficient vary over a large range for reasons that remain largely unexplained."

The relationship of the various available data sets on the feed-to-milk transfer coefficient was discussed in one of the last HEDR Project public meetings in Seattle. The subject was extensively discussed in that meeting by external reviewers and the public, and these values were accepted and used by the HEDR team.

At the Seattle meeting, additional reviews of this coefficient published by other groups were discussed. One of the most interesting was prepared as a joint effort between the U.S. Nuclear Regulatory Commission and the Commission of European Communities (NRC/EC 1997). This study grew out of an attempt to develop credible and traceable uncertainty distributions for the input variables in environmental assessment computer codes being developed by these entities. The study used expert elicitation methods to determine the ranges and bounds for a number of parameters, one of which was the feed-to-milk transfer coefficient for individual cows. For this multinational study, an elicitation procedure was developed, tested and clarified. Internationally recognized experts were selected using a common set of criteria. Probability training exercises were conducted to establish ground rules and set the initial and boundary conditions. The experts developed their distributions independently of each other. For the feed-to-milk transfer factor, 10 experts provided inputs. The experts were asked to provide their estimates of the fifth percentile, median, and ninety-fifth percentile values for the parameter. They provided

extensive rationale and supporting references, which are included in the final report. The raw estimates for each expert are provided in Table 5-1, along with the corresponding HEDR values (derived at the appropriate percentiles from the distribution in Snyder et al. 1994).

The NRC/EC report also developed an aggregated ranges provided by the experts into a single cumulative distribution. The overall ranges of distributions described by the various experts are compared to the aggregated value and to the HEDR distribution in Figure 1. (Note that the experts were only asked to provide 5% to 95% ranges, the HEDR distribution was truncated at the 1 and 99% levels). From Figure 5-1, it can be seen that the HEDR distribution generally falls within the upper portion of the ranges defined by the experts. The lower half of the HEDR range is somewhat higher, up to a factor of 5 higher than the experts' aggregated value at the 5% value. However, the upper portion of the range is essentially the same, from about the 50% to the 95% values. The HEDR values are actually lower than the experts' aggregate value beyond about the 85th percentile

The HEDR model used a herd-averaged transfer value to describe the general transfer of ^{131}I in milk within the commercial milk distribution system. This is because pooling milk from many individual cows has the result of averaging the transfer factor. The HEDR herd-averaged value was obtained from the distribution of individual cows' transfer factors. The average of the HEDR distribution is 0.012 day/liter, which was assigned a

Table 5-1.Various experts' estimates of the ^{131}I feed-to-milk transfer factor, d/L (NRC/EC 1997)

Expert	*5th percentile*	*Median*	*95th percentile*
H	0.001	0.01	0.04
I	0.001	0.007	0.03
J	0.001	0.01	0.04
K	0.001	0.01	0.035
L	0.001	0.011	0.034
M	0.001	0.005	0.01
N	0.0005	0.005	0.05
O	0.002	0004	0.01
P	0.002	0.004	0.018
Q	0.002	0.01	0.02
HEDR	0.0028	0.0092	0.032

small uncertainty of a standard deviation of 0.002 day/liter. This value may be compared with the average of the expert elicitation process described above. The average of the expert elicitation process is about 0.015 day/liter. It may also be compared against other comparable values used in recent assessments. The International Union of Radioecologists (IUR/IAEA 1994) reports that the range of minimum to maximum values of F_m reported in the radioecological literature is about 1×10^{-3} to 3.5×10^{-2} day/liter. The IUR considers a "typical" value, i.e., one most likely to occur, to be about 0.01 day/liter. Studies referenced in the NRC/EC (1997) study include some for the computer codes ECOSYS (Muller et al. 1993) and MARC (Jones, Mansfield, and Crick 1995). These are both post-Chernobyl studies that attempted to review the pertinent literature. The HEDR herd distribution is compared to the ECOSYS, MARC, and NRC/EC values in Figure 5-2. The mean value for the ECOSYS distribution is 0.0055 day/liter, and for the MARC distribution is 0.011 day/liter. It can be seen that the HEDR, IUR/IAEA, and MARC results are all very close; the ECOSYS result is about one-half these others – and close to the results referenced in the National Academy review.

The HEDR value is also similar to that used in the estimation of iodine exposures from Nevada Test Site fallout in the PATHWAY model (Whicker and Kirchner 1987; Whicker et al. 1996). A mean of the transfer factor of 0.0084 day/liter can be derived for this model (Breshears et al. 1989), with a lognormal distribution with a 95% confidence interval from 0.005 to 0.14.

All of the studies described here were performed after the Chernobyl accident in 1986 and included post-Chernobyl results in their determination of distributions. It has been noted that the Chernobyl situation appears to be unique, and that concentrations of ^{131}I observed in milk after the accident were somewhat lower than expected on the basis of previous measurements (Kirchner 1994). In light of the recent studies, it appears possible that the distribution selected by HEDR could possibly have included some lower values with low probabilities, but that the average and upper range is in line with much of current understanding. However, when using parameters with relatively wide distributions, the average result is dominated by the higher values, which would not change were the HEDR selection to have included more low values.

Overall, the selection made appears to have been reasonable and prudent, particularly in light of pressure at the time from the public and the HEDR Technical Steering Panel to have higher values (see for example Price 1994, where herd-averaged values of 0.0126 for commercial and 0.0139 for backyard cows is suggested).

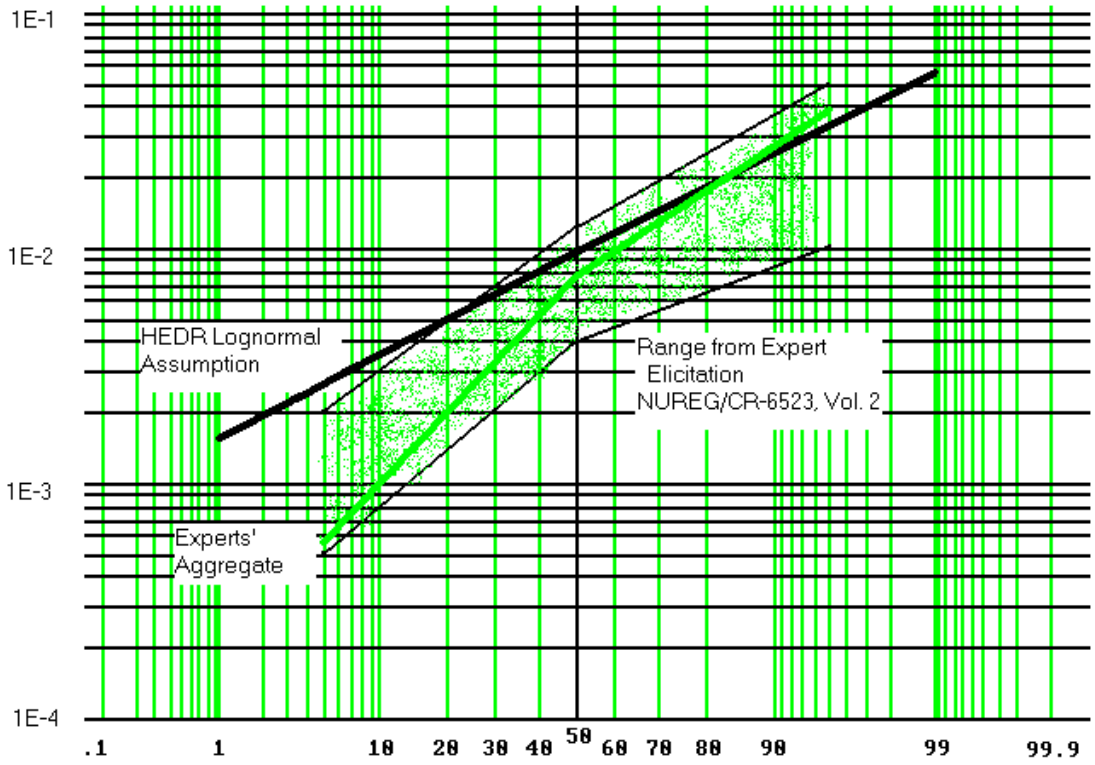

Figure 5-1. Comparison of HEDR feed-to-milk transfer factor to that developed through expert elicitation

5.1 References for Section 5

Breshears, D.D., T.B. Kirchner, M.D. Otis, and F.W. Whicker, 1989. "Uncertainty in Predictions of Fallout Radionuclides in Foods and of Subsequent Ingestion," Health Physics; 57(6):943-953

International Union of Radioecologists and International Atomic Energy Agency (IUR/IAEA), 1994. Handbook of Parameter Values for the Prediction of Radionuclide Transfer in Temperate Environments, Technical Reports Series No. 364, IAEA, Vienna.

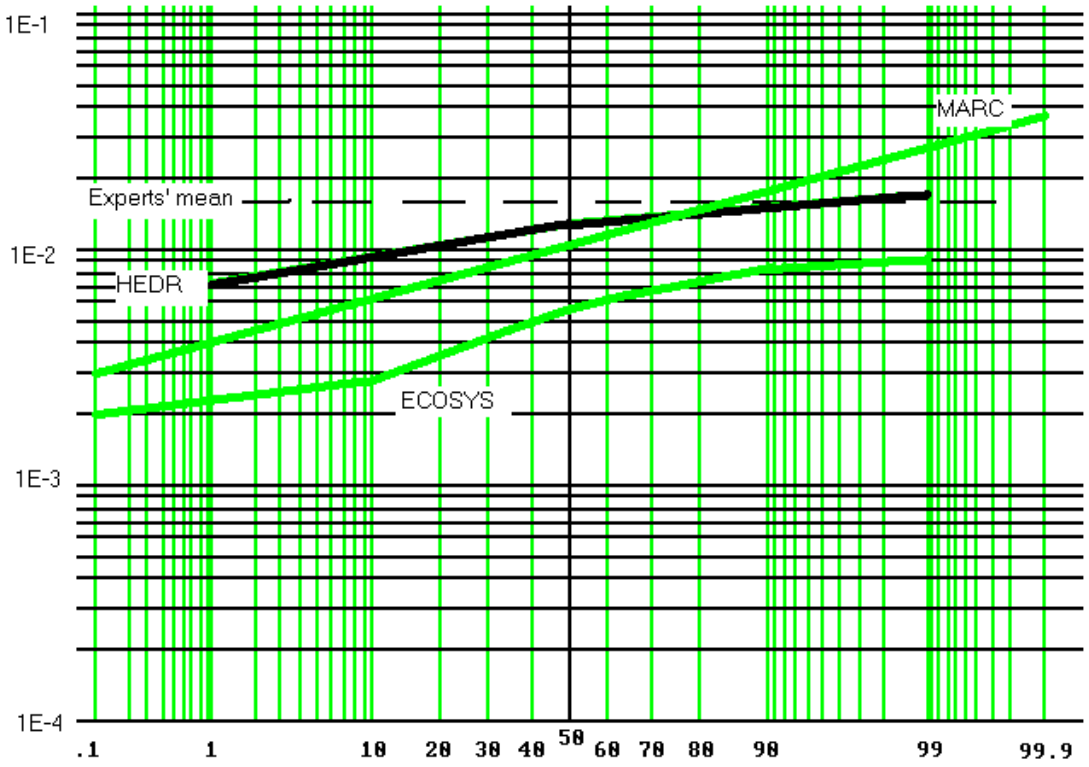

Figure 5-2. Comparison of HEDR feed-to-milk transfer factor with those used in other recent assessments

Jones, J.A., P.A. Mansfield, and M.J. Crick. 1995. Uncertainty Analysis of the Predicted Consequences of Nuclear Accidents using the NRPB Code MARC-2A, NRPB-R274, Chilton, England

Kirchner, G. 1994. "Transport of Iodine and Cesium Via the Grass-Cow-Milk Pathway After the Chernobyl Accident," Health Physics;66(6):653-665

Muller, H., W. Friedland, et al., "Uncertainty in the Ingestion Dose Calculation," Radiation Protection Dosimetry, 50 (1-4), 353-357, 1993.

Price, D.W. 1994. Dairy Cow Feeding Regimes for Representative Doses, Special Report, Technical Steering Panel of the Hanford Environmental Dose Reconstruction Project

Snyder, S.F., W.T. Farris, B.A. Napier, T.A. Ikenberry, and R.O. Gilbert. 1994. Parameters Used in the Environmental Pathways and Radiological Dose Modules (DESCARTES, CIDER, and CRD) of the Hanford Environmental Dose Reconstruction Integrated Codes (HEDRIC). PNWD-2023 HEDR Rev. 1, Battelle Pacific Northwest Laboratories, Richland, Washington

U.S. Nuclear Regulatory Commission and Commission of European Communities (NRC/EC), 1997. Probabilistic Accident Consequence Uncertainty Analysis; Food Chain Uncertainty Assessment, NUREG/CR-6523, Volumes 1 and 2, Nuclear Regulatory Commission, Washington, D.C.

Whicker, F.W., T.B. Kirchner, L.R. Anspaugh, and Y.C. Ng, 1996. "Ingestion of Nevada Test Site Fallout: Internal Dose Estimates," Health Physics;71(4):477-486

Whicker, F.W., and T.B. Kirchner, 1987. "PATHWAY: A Dynamic Food-Chain Model to Predict Radionuclide Ingestion after Fallout Deposition," Health Physics;52(6):717-737

6. Fetal Dose Conversion Factors

The National Academy of Sciences review of the HTDS dosimetry results noted that the uncertainty estimates accompanying the individual HTDS doses appeared to be too low. The geometric standard deviations of some doses were estimated to be as low as 1.4, while the geometric standard deviation (GSD) of the dose conversion factors themselves was about 2.0 (Snyder et al. 1994). The NAS reviewers noted that the doses estimated for reference individuals in the HEDR project had uncertainties with GSDs of 2 or greater (Farris et al. 1994). The NAS recommended that the HTDS authors explain why the uncertainty ranges were so narrow for this class of doses.

This comment induced the HTDS staff to review the input parameters used in the calculations. All dose conversion factor values that were used are documented in Snyder et al. (1994). All of the internal dose conversion factors in Snyder et al. (1994) have GSDs of 2 or greater, with one exception. The exception is the prenatal dose factor – the one applied to individuals in the period prior to birth. The description of that factor implied a GSD of 2 would be appropriate, but a triangular approximation using one-half to twice the central value was used (Snyder et al. 1994, page 6.58). Because none of the reference dose calculations prepared for the HEDR final reports used this parameter, this had no impact on the HEDR calculations and the parameter as input to the codes was not seriously reviewed. The HTDS staff acquired the HEDR code CIDER with its associated databases, and also did not seriously question this selection until it was pointed out by the NAS. This narrow distribution would result in overall narrowed uncertainties for individuals who were primarily exposed *in utero*.

Upon the discovery of the nature of this parameter by HTDS, the remaining HEDR staff prepared a new input file of the prenatal dose factors using the central value of Snyder et al. supplemented with a GSD of 2. This updated file was supplied in February 2000 to staff of the Fred Hutchinson Cancer Research Center, the Centers for Disease Control and Prevention, and the Individual Dose Assessment project. It has been used for all subsequent calculations and recalculations.

6.1 References for Section 6

Snyder, S.F., W.T. Farris, B.A. Napier, T.A. Ikenberry, and R.O. Gilbert. 1994. Parameters Used in the Environmental Pathways and Radiological Dose Modules (DESCARTES, CIDER, and CRD) of the Hanford Environmental Dose Reconstruction Integrated Codes (HEDRIC). PNWD-2023 HEDR Rev. 1, Battelle Pacific Northwest Laboratories, Richland, Washington

Farris, W.T., B.A. Napier, T.A. Ikenberry, J.C. Simpson, and D.B. Shipler. 1994. Atmospheric Pathway Dosimetry Report, 1944-1992, Hanford Environmental Dose Reconstruction Project, PNWD-2228 HEDR, Battelle Pacific Northwest Laboratories, Richland, Washington

7. CIDER modifications

Several small changes were made to the CIDER (Ouderkirk and Eslinger 1993; Eslinger et al. 1994) dose calculation computer code.

7. 1 Hardware requirements for new version of CIDER.

The original version of the CIDER code was developed for the large HEDR Sun computer. That machine was decommissioned after the HEDR project ended, and neither Battelle Pacific Northwest Laboratories nor Fred Hutchinson Cancer Research Center Hanford Thyroid Disease Study (HTDS) have comparable machines available. Battelle has implemented other modules of the HEDR codes on a PC with capabilities that are modest by current standards (512 MB of memory, 18GB hard drive [much less is required to run CIDER], 233 Mhz). It was agreed that further revisions would be made on a PC version, which HTDS could then run in-house. This benefits HTDS by removing the difficulties inherent in transferring scenario files and dose estimation results back and forth from the Centers for Disease Control and Prevention (CDC) system. It should also be a fairly simple matter for HTDS to identify or acquire a PC adequate to run the new version of CIDER. The adoption of a PC-based version will also be generally beneficial by providing a more portable system. However it will also require CDC to adopt the new version as the current standard.

7.2 Internal correlations

The original CIDER code performed no stochastic variable selection; all realizations of all parameters were input from externally created files. This was done for simplicity in CIDER and for repeatability of the calculations. This has no influence on any individual dose calculation; however, when analyzing the entire set of HTDS subjects, it can result in undesirable internal correlations between individuals. The correlations occur because the random variables are always selected in the same order for the realizations, which causes statistically-observable patterns in the results. The patterns are artifacts of the calculation process that interfere with the overall analyses. The CIDER code was modified to allow randomization of the order of selection of stochastic dose conversion factors. The same external files are accessed, but the order of use of the values is now permuted on the basis of an input key, which may be made unique for every person.

7.3 Uncertainties in Reported Dietary Intakes

The National Academy of Science review of the HTDS noted that "The HTDS did not take into account the uncertainties associated with the recall – 5 decades after the period of exposure – of the origin of milk, the milk consumption rate, or changes in residence. That is a serious flaw of the methodology…" The HTDS protocol was widely debated when it was designed, and public sentiment at the time was strongly against any modification of the reported values. Therefore, at the Technical Steering Panel's direction, the CIDER code was designed to accept the respondents' input without modifications.

No data are available from the Computer-Aided Telephone Interview (CATI) to assess the uncertainties in the reported information. The largest set of detailed information on American food consumption patters as functions of age, sex, location, and lifestyle come from the U.S. Department of Agriculture 1977-78 Nationwide Food Consumption Survey (USDA 1983). This information was adapted for the CIDER code and, through a backcasting technique, a series of default reference diets were prepared (Anderson 1993). These reference diets were used for all HEDR project example calculations, and were used to support the HTDS calculations for foods not reported by the HTDS respondents. Essentially all that is available about the variability of American intakes of various foods is summarized in the reference diet tables.

A practical method for assigning uncertainties to the dietary factors in CIDER is to apply the uncertainty for dietary factors from the reference diets used in default calculations to the reported values from the CATI. However this approach applies only to dietary consumption data, since the use of reference diet value sets $\{R_{p,1}, \ldots, R_{p,100}\}$ is already built into CIDER. This does not apply to the remaining input parameters: distributions of milk/food products among sources, residence history (locations and periods of residence), family cow feeding regimes, and breast-feeding characteristics (yes/no, wean date). Major structural modifications of CIDER would be required to incorporate uncertainty of these input parameters. Therefore it was agreed that only dietary factors would be addressed.

Several ideas were developed for incorporating uncertainties about dietary consumption levels reported from the CATI for HTDS participants. There is no simple and

direct way to do this, because the data were collected with the explicit intention of using it directly. It was determined that the most defensible approach would be the simplest approach that allowed investigation of the impact of various options on the final dose/response results. In a telephone conversation with Dr. Ken Kopecky, FHCRC, on July 28, 2000, the following approach was outlined. The purpose of this approach is to allow a wide degree of flexibility in modeling these uncertainties, so that their impact on HTDS dose estimates and dose response results can be explored.

The approach that was implemented proceeds as follows:

Specify a scaling factor $SF_0 \geq 0$, which controls the handling of reported consumption values of 0: if $SF_0 = 0$, no uncertainty will be applied to reported values of 0; if $SF_0 > 0$, then uncertainty will be applied.

Specify the value of two parameters:

- $SF \geq 0$, a scaling factor for the application of reference diet uncertainties, and
- $G \geq 0$, a geometric standard deviation for the application of lognormal uncertainties.

For each of these parameters, specifying a value of 0 indicates that the corresponding uncertainty will not be applied to the reported consumption values. Since at most one type of uncertainty will be applied, an error is reported and processing stops if both SF and G are assigned values greater than 0. The possible combinations of the three parameters are summarized in Table 7-1.

The implementation of the transformation proceeds as follows:

If $SF > 0$ and $G = 0$, reference diet uncertainties are obtained by transforming the reported consumption value R_p into 100 realizations $r_{p,1}, \ldots, r_{p,100}$ as

$$r_{p,i} = \begin{cases} SF_0 \times m_p \times (R_{p,j[i]} / m_p)^{SF} & \text{if } R_p = 0 \\ R_p \times (R_{p,j[i]} / m_p)^{SF} & \text{if } R_p > 0 \end{cases}$$

where

$i = 1, \ldots, 100$,

$\{R_{p,1}, \ldots, R_{p,100}\}$ is the reference diet, indexed by realizations 1, …, 100,

Table 7-1. CIDER Input Options for Handling Uncertainties in Reported Consumption

SF_0	SF	G	Handling of uncertainty and reported values of 0
0	0	0	No uncertainty is applied to any reported consumption values; all reported values (including 0s) are left unchanged
> 0	0	0	No uncertainty is applied to reported consumption values; reported values of 0 are replaced with positive values with no uncertainty
0	> 0	0	Reference diet uncertainties are applied to reported consumption values > 0; reported values of 0 are left as 0 with no uncertainty
> 0	> 0	0	Reference diet uncertainties are applied to reported consumption values > 0, and to positive values substituted for reported values of 0
0	0	> 0	Lognormal uncertainties are applied to reported consumption values > 0; reported values of 0 are left as 0 with no uncertainty
> 0	0	> 0	Lognormal uncertainties are applied to reported consumption values > 0, and to positive values substituted for reported values of 0
0	> 0	> 0	Not permissible
> 0	> 0	> 0	Not permissible

{j[1], …, j[100]} is a pseudorandomly generated permutation of the indices 1, …, 100, and

m_p is the mean of $R_{p,1}$, …, $R_{p,100}$.

Note that this transformation has the following effects:

- If the reported value R_p is positive, then $r_{p,i} = 0$ whenever $R_{p,j[i]} = 0$. In other words, any zeroes present in the reference diet will be reflected in the uncertainty applied to the reported value.

- If the reported value R_p is zero and $SF_0 > 0$, then R_p is replaced by $SF_0 \times m_p$, which can be made "small" by a sufficiently small choice of SF_0. As above, any zeroes present in the reference diet will be reflected in the uncertainty applied to the reported value.

- If $SF_0 = 0$, then no uncertainty is applied to reported values of zero (i.e., $R_p = 0$ is transformed into $r_{p,1} = r_{p,2} = \ldots = r_{p,100} = 0$).

- If $SF > 0$, then the GSD of $r_{p,1}, \ldots, r_{p,100}$ for $R_p > 0$ (and for all R_p if $SF_0 > 0$) is g^{SF} where g is the GSD of the reference diet $\{R_{p,1}, \ldots, R_{p,100}\}$; thus if $SF = 1$, the uncertainty about reported consumption values has the same GSD as the corresponding reference diet.

If $SF = 0$ and $G > 0$, reference diet uncertainties are obtained by transforming the reported consumption value R_p as

$$r_{p,i} = \begin{cases} S_i \times SF_0 \times m_p & \text{if } R_p = 0 \\ S_i \times R_p & \text{if } R_p > 0 \end{cases}$$

where

$\{S_1, \ldots, S_{100}\}$ is a set of pseudorandomly generated realizations of a lognormally distributed random variable with mean 1 and geometric standard deviation G.

Note that if $SF_0 > 0$, then $r_{p,i} > 0$ for all i; in other words, all of the realizations $r_{p,i}$ are positive, even if the reported consumption value is 0. If $SF_0 = 0$, then $r_{p,i} > 0$ for all i if $R_p > 0$, while $r_{p,i} = 0$ for all i if $R_p = 0$; that is the realizations $r_{p,i}$ are all either 0 or positive, depending on whether R_p is 0 or positive, respectively.

The lognormal variates $S_1, \ldots, S_{100}$ are generated as a new set of 100 realizations $\{S_1, \ldots, S_{100}\}$ each time.

A minor difficulty with the two approaches defined above is that in the reference diets there are some food types for which all default realizations are zero. That is, no person in 1977 of that age/sex/season/urbanization combination reported eating that particular food. As a result, the mean of the reference diet distribution is zero, which would cause problems with undefined variables for some combinations of input. Therefore, an additional step of establishing surrogate diets for those few food categories was undertaken. The cases of all-zero food consumption occur only for some combinations of age/season for very young children. The only foods for which the problem occurs are leafy vegetables, eggs, and

poultry. Because there are always combinations of age/sex/season/urbanization that are closely related (rural versus urban, or summer versus fall) that do have non-zero results, it was felt better to use the closest approximation than to attempt to create another diet category. A diet surrogate matrix was established that cross-referenced each food type in each reference diet with either itself or a similar non-zero set of entries. This matrix was added to the internal CIDER data so that the several versions of the diet file would not need to be changed. The matrix is only invoked when one or more of SF_0, SF, or G is non-zero. The contents and format of the addition are shown in Table 7-2. Entries are indexed by row and column; entries indicate which reference diet the code should access when looking for a non-zero set of data for a particular food type. Note that only 12 transfers are indicated.

The algorithms and options described above were added to the CIDER code. The resulting changes were tested independently and together, and the results compared to equivalent results from the original, unmodified code. Additional observational and hand-calculation tests were made to ensure that the code processes the options correctly. Additional tests were run by FHCRC staff to verify the changes. Code development and testing records have been maintained and are available in project records.

7.3 References for Section 7

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Ouderkirk, S.J., P.W. Eslinger. 1993. Software Design Description for the CIDER Dose Estimation Computer Code, Battelle Pacific Northwest Laboratories, Richland, Washington.

U.S. Department of Agriculture (USDA). 1983. Food Consumption: Households in the United States, Seasons, and Years 1977-1978. National Food Consumption Survey 1977-1978, Report No. H-6, Human Nutrition Information Service, Consumer Nutrition Division. U.S. Government Printing Office, Washington, D.C.

Table 7-2. Non-zero diet pointers for reference diet file

1. f-milk	2. s-milk	3. l-veg	4. o-veg	5. fruit	6. grain	7. eggs	8. beef	9. poultry
1	1	1	1	1	1	1	1	1
2	2	17*	2	2	2	107	2	2
3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9
10	10	10	10	10	10	10	10	10
11	11	11	11	11	11	11	11	11
12	12	12	12	12	12	12	12	12
13	13	13	13	13	13	13	13	13
14	14	14	14	14	14	14	14	14
15	15	15	15	15	15	15	15	15
16	16	16	16	16	16	16	16	16
17	17	17	17	17	17	77	17	17
18	18	18	18	18	18	18	18	18
19	19	19	19	19	19	19	19	19
20	20	20	20	20	20	20	20	20
21	21	21	21	21	21	21	21	21
22	22	22	22	22	22	22	22	22
23	23	23	23	23	23	23	23	23
24	24	24	24	24	24	24	24	24
25	25	25	25	25	25	25	25	25
26	26	26	26	26	26	26	26	26
27	27	27	27	27	27	27	27	27
28	28	28	28	28	28	28	28	28
29	29	29	29	29	29	29	29	29
30	30	30	30	30	30	30	30	30
31	31	31	31	31	31	31	31	31
32	32	17	32	32	32	92	32	32
33	33	33	33	33	33	33	33	33
34	34	34	34	34	34	34	34	34
35	35	35	35	35	35	35	35	35
36	36	36	36	36	36	36	36	36
37	37	37	37	37	37	37	37	37
38	38	38	38	38	38	38	38	38
39	39	39	39	39	39	39	39	39
40	40	40	40	40	40	40	40	40
41	41	41	41	41	41	41	41	41
42	42	42	42	42	42	42	42	42
43	43	43	43	43	43	43	43	43
44	44	44	44	44	44	44	44	44
45	45	45	45	45	45	45	45	45
46	46	46	46	46	46	46	46	46
47	47	17	47	47	47	107	47	47
48	48	48	48	48	48	48	48	48

1. f-milk	2. s-milk	3. l-veg	4. o-veg	5. fruit	6. grain	7. eggs	8. beef	9. poultry
49	49	49	49	49	49	49	49	49
50	50	50	50	50	50	50	50	50
51	51	51	51	51	51	51	51	51
52	52	52	52	52	52	52	52	52
53	53	53	53	53	53	53	53	53
54	54	54	54	54	54	54	54	54
55	55	55	55	55	55	55	55	55
56	56	56	56	56	56	56	56	56
57	57	57	57	57	57	57	57	57
58	58	58	58	58	58	58	58	58
59	59	59	59	59	59	59	59	59
60	60	60	60	60	60	60	60	60
61	61	61	61	61	61	61	61	61
62	62	62	62	62	62	107	62	62
63	63	108	63	63	63	63	63	63
64	64	64	64	64	64	64	64	64
65	65	65	65	65	65	65	65	65
66	66	66	66	66	66	66	66	66
67	67	67	67	67	67	67	67	67
68	68	68	68	68	68	68	68	68
69	69	69	69	69	69	69	69	69
70	70	70	70	70	70	70	70	70
71	71	71	71	71	71	71	71	71
72	72	72	72	72	72	72	72	72
73	73	73	73	73	73	73	73	73
74	74	74	74	74	74	74	74	74
75	75	75	75	75	75	75	75	75
76	76	76	76	76	76	76	76	76
77	77	92	77	77	77	77	77	77
78	78	78	78	78	78	78	78	78
79	79	79	79	79	79	79	79	79
80	80	80	80	80	80	80	80	80
81	81	81	81	81	81	81	81	81
82	82	82	82	82	82	82	82	82
83	83	83	83	83	83	83	83	83
84	84	84	84	84	84	84	84	84
85	85	85	85	85	85	85	85	85
86	86	86	86	86	86	86	86	86
87	87	87	87	87	87	87	87	87
88	88	88	88	88	88	88	88	88
89	89	89	89	89	89	89	89	89
90	90	90	90	90	90	90	90	90
91	91	91	91	91	91	91	91	91
92	92	92	92	92	92	92	92	92
93	93	93	93	93	93	93	93	93
94	94	94	94	94	94	94	94	94
95	95	95	95	95	95	95	95	95
96	96	96	96	96	96	96	96	96
97	97	97	97	97	97	97	97	97
98	98	98	98	98	98	98	98	98

1. f-milk	2. s-milk	3. l-veg	4. o-veg	5. fruit	6. grain	7. eggs	8. beef	9. poultry
99	99	99	99	99	99	99	99	99
100	100	100	100	100	100	100	100	100
101	101	101	101	101	101	101	101	101
102	102	102	102	102	102	102	102	102
103	103	103	103	103	103	103	103	103
104	104	104	104	104	104	104	104	104
105	105	105	105	105	105	105	105	105
106	106	61	106	106	106	106	106	106
107	107	92	107	107	107	107	107	107
108	108	108	108	108	108	108	108	108
109	109	109	109	109	109	109	109	109
110	110	110	110	110	110	110	110	110
111	111	111	111	111	111	111	111	111
112	112	112	112	112	112	112	112	112
113	113	113	113	113	113	113	113	113
114	114	114	114	114	114	114	114	114
115	115	115	115	115	115	115	115	115
116	116	116	116	116	116	116	116	116
117	117	117	117	117	117	117	117	117
118	118	118	118	118	118	118	118	118
119	119	119	119	119	119	119	119	119
120	120	120	120	120	120	120	120	120

* Shaded cells indicate sets of all-zero consumption realizations, and the entries therein indicate to which alternative set of data the CIDER code refers.

Analysis of Mortality in the HTDS Cohort

An analysis was conducted to investigate whether the mortality experience in the HTDS cohort overall was unusually high, relative to what would be expected based on the mortality experience of the population of the same region over the same time period. Additional analyses were conducted to determine whether there was any indication of an excess in mortality in the HTDS cohort from conditions that might be related to one or more of the primary outcomes of interest.

In this study, 527 (10.1%) of the 5199 individuals originally identified were confirmed as deceased and an additional 16 (0.3%) were located alive but died before participating in the HTDS. A death certificate was obtained for 504 (93% of the 543) in order to determine the cause of death for each person. In the remaining 39, cause of death was ascertained from the source of information which confirmed the death (usually a close relative).

Included in the mortality analyses were all living located subjects, as well as all deceased subjects for whom both age and cause of death could be ascertained. Causes of deaths for cohort members were crosstabulated by age at death. Standardized mortality ratios (SMRs) were calculated for each cause of death to assess whether the morality experience of the selected cohort differed from what would be expected based on the mortality experience of the population of the State of Washington over the same period of follow-up. The calculation of SMRs and their confidence interval are described in Breslow and Day (1). The person-years for the Hanford cohort were calculated based on a program developed by Wood, Richardson, and Wing (2). Inexact death dates in the Hanford cohort were assigned values at the midpoint of the range, i.e., if the month and year was known but not the day, it was assigned as 15; if only the year was known the month and day were assigned as July 1, etc.

The death rates for the population of Washington State (i.e., the rates to which the mortality experience of the selected cohort was compared) were obtained from historical mortality data and other data published by or otherwise available from the National Center for Health Statistics, the State of Washington, and the U.S. Bureau of the Census. For the years 1940-1965 the mortality data were based on tables from Vital Statistics of the United States. The 1941 data were applied to 1940, since no appropriate data from 1940 could be found. For the years 1970-1980 and 1990, the source of the mortality data was Washington State death files previously obtained by the HTDS to perform matches to the study cohort. These files only had the year of death and not the month and day, and thus date of death was assigned as July 1. For 1985 and 1995, the source of the mortality data was Washington State death files from a CDROM produced by the State of Washington. Population estimates for the State of Washington were based on the U.S. Census, using interpolation for the years between censuses.

Tables Appendix 23-1 and Appendix 23-2 show the distribution of deaths in the HTDS cohort according to eleven categories of cause of death for females and males, respectively. There were 199 deaths in females and 344 deaths in males, with no known age of death for two of the males. For both sexes, the largest proportion of deaths occurred under one year of age (36% for both males and females). Most of these deaths were due to conditions in the perinatal period or congenital anomalies. Approximately 31% of the deaths in females were due to these two causes, as were approximately 27% of the deaths in males.

Table Appendix 23-1. Cause of Death by Age at Death for Females

	Age at Death (years)									
Cause of Death	<1	1-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	Total
Infectious/parasitic	2	3	0	0	0	0	0	0	0	5
Malignant Neoplasms	0	1	1	1	1	1	6	20	11	42
Diabetes	1	0	0	0	0	0	0	1	2	4
Cardiovascular Disease	0	0	0	0	1	0	2	11	2	16
Pneumonia & influenza	3	1	0	0	0	0	1	0	0	5
Gastrointestinal disorders	0	0	0	0	0	0	0	0	0	0
Congenital Anomalies	13	1	1	0	0	1	0	0	0	16
Conditions in the perinatal period	45	0	0	0	0	0	0	0	0	45
External causes of injury/poisoning	1	9	3	3	3	4	9	4	3	39
All other causes	7	5	3	0	2	2	2	3	3	27
Total	72	20	8	4	7	8	20	39	21	199

Table Appendix 23-2. Cause of Death by Age at Death for Males

	Age at Death (years)									
Cause of Death	<1	1-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	Total
Infectious/parasitic	9	2	1	1	0	0	0	6	1	20
Malignant Neoplasms	0	1	1	0	3	4	3	14	3	29
Diabetes	1	1	0	0	0	0	1	1	0	4
Cardiovascular Disease	0	0	0	0	1	1	5	22	10	39
Pneumonia & influenza	13	1	0	0	0	0	0	0	0	14
Gastrointestinal disorders	1	0	0	0	0	0	1	6	0	8
Congenital anomalies	21	1	1	0	0	2	0	1	0	26
Conditions in the perinatal period	65	0	0	0	0	0	0	0	0	65
External causes of injury/poisoning	5	7	3	3	7	34	24	19	4	106
All other causes	8	3	0	1	2	3	4	4	6	31
Total	123	16	6	5	13	44	38	73	24	342

Note: 2 males, for whom the date of death is unknown, died of other causes and are omitted from this table.

Table Appendix 23-3 shows standardized mortality ratios for the ten cause of death categories by sex. Overall, there was no increase in total mortality over what would be expected based on the mortality experience of the population of Washington State during the same time period (SMR = 0.97; 95% Confidence Interval (CI) = 0.89, 1.06). This was true for both females (SMR = 0.96) and males (SMR = 0.98). However, there was an excess in deaths due to conditions of the perinatal period (SMR = 1.69, 95% CI = 1.39, 2.04), which was found in both females (SMR = 1.70) and males (SMR = 1.68).

Table Appendix 23-3. Standardized Mortality Ratio (SMR), by Cause of Death and Sex

	Female		Male		Total	
Cause of Death	SMR	95% CI	SMR	95% CI	SMR	95% CI
Infectious/parasitic	0.25	0.08, 0.59	0.51	0.31, 0.79	0.42	0.27, 0.63
Malignant neoplasms	1.16	0.84, 1.57	0.84	0.56, 1.20	1.00	0.78, 1.26
Diabetes	1.05	0.29, 2.69	0.76	0.21, 1.94	0.88	0.38, 1.73
Cardiovascular disease	1.20	0.68, 1.94	1.27	0.90, 1.73	1.24	0.94, 1.62
Pneumonia & influenza	0.38	0.12, 0.88	0.80	0.44, 1.34	0.62	0.37, 0.96
Gastrointestinal disorders.	0	--	1.09	0.47, 2.15	0.67	0.29, 1.31
Congenital anomalies	1.11	0.64, 1.81	1.26	0.82, 1.85	1.20	0.86, 1.62
Conditions of perinatal period	1.70	1.24, 2.27	1.68	1.30, 2.14	1.69	1.39, 2.04
External causes of injury/poisoning	1.20	0.85, 1.64	1.12	0.92, 1.36	1.14	0.96, 1.35
All other causes	0.66	0.43, 0.96	0.50	0.34, 0.71	0.56	0.43, 0.73
Total	0.96	0.84, 1.11	0.98	0.88, 1.09	0.97	0.89, 1.06

Analyses were conducted to investigate whether there was any excess in mortality according to geostratum of birth. Table Appendix 23-4 shows standardized mortality ratios according to geostratum, by sex. The only excess in mortality was observed among persons from the geostrata defined by birth in Franklin County (SMR = 1.61, 95% CI = 1.15, 2.20). This excess mortality in Franklin County was found for males (SMR = 1.66, 95% CI = 1.09, 2.44), but was only suggestive for females (SMR = 1.53, 95% CI = 0.83, 2.56).

Table Appendix 23-4. Standardized Mortality Ratio (SMR) for All Causes of Death, by Geostratum and Sex

	Female		Male		Total	
Geostratum	SMR	95% CI	SMR	95% CI	SMR	95% CI
Richland	0.81	0.46, 1.31	0.69	0.44, 1.04	0.74	0.52, 1.01
Pasco/Kennewick	1.10	0.85, 1.40	1.02	0.84, 1.23	1.05	0.90, 1.22
Walla Walla (city)	1.01	0.58, 1.65	0.79	0.49, 1.20	0.87	0.61, 1.20
Benton County	1.09	0.80, 1.44	1.13	0.90, 1.40	1.11	0.93, 1.32
Franklin County	1.53	0.83, 2.56	1.66	1.09, 2.44	1.61	1.15, 2.20
Walla Walla County	0.43	0.18, 0.84	0.73	0.46, 1.10	0.62	0.42, 0.88
Okanogan County	0.85	0.34, 1.75	0.98	0.52, 1.67	0.93	0.57, 1.43
Ferry/Stevens Counties	0.95	0.41, 1.86	0.96	0.51, 1.63	0.95	0.59, 1.46
Adams County	0.69	0.38, 1.16	0.86	0.58, 1.23	0.80	0.58, 1.07
Total	0.96	0.84, 1.11	0.98	0.88, 1.09	0.97	0.89, 1.06

In an attempt to see whether the observed excesses in mortality were concentrated among persons born around the time of the peak releases from Hanford (i.e., 1945 and 1946), a number of analyses were

repeated separately for the birth cohorts defined by the period 1940-44, and 1945-46. Table Appendix 23-5 shows essentially no difference in mortality between the 1945-46 birth cohorts and the 1940-1944 birth cohorts.

Table Appendix 23-5. Standardized Mortality Ratio (SMR) for All Causes of Death, by Birth Year Category and Sex

	Female		Male		Total	
Birth Year	SMR	95% CI	SMR	95% CI	SMR	95% CI
1940-1944	1.00	0.85, 1.17	0.95	0.83, 1.08	0.97	0.88, 1.07
1945-1946	0.86	0.63, 1.16	1.06	0.86, 1.29	0.99	0.83, 1.16

When considering mortality by birth year within geostrata, there was no evidence that the later birth cohorts experienced a greater excess in mortality in those counties with little or no excess mortality overall (Table Appendix 23-6). In Franklin County the excess mortality relative to expected was a little higher for the 1945-46 birth cohort than the 1940-1944 birth cohort, but this difference was not statistically significant.

Table Appendix 23-6. Standardized Mortality Ratio (SMR) for All Causes of Death, by Geostratum and Birth Year Category

	1940-1944		1945-1946	
Geostratum	SMR	95% CI	SMR	95% CI
Richland	0.69	0.37, 1.18	0.76	0.50, 1.12
Pasco/Kennewick	1.01	0.85, 1.19	1.22	0.86, 1.67
Walla Walla (city)	1.00	0.66, 1.46	0.64	0.31, 1.18
Benton County	1.05	0.86, 1.27	1.45	0.96, 2.11
Franklin County	1.53	1.03, 2.18	1.95	0.94, 3.58
Walla Walla County	0.56	0.33, 0.88	0.73	0.39, 1.24
Okanogan County	0.72	0.34, 1.32	1.31	0.63, 2.41
Ferry/Stevens Counties	1.33	0.79, 2.10	0.35	0.07, 1.03
Adams County	0.78	0.56, 1.07	0.92	0.25, 2.34
Total	0.97	0.88, 1.07	0.99	0.83, 1.16

Birth year analyses were also conducted for the two cause of death categories shown to have the greatest excess over expected in the overall analysis (congenital anomalies and conditions of the perinatal period). Table Appendix 23-7 shows that for causes attributed to conditions of the perinatal period, the excess in mortality was considerably higher for the 1945-46 birth cohort (SMR = 2.3, 95% CI = 1.7, 3.0). This pattern was not seen for congenital anomalies. For the two causes combined, there was approximately an 87% excess in mortality over expected for the 1945-46 birth cohort that was statistically significant. In comparison, the excess for these two causes for the 1940-44 birth cohort was approximately 37%, and was also statistically significant.

Table Appendix 23-7. Standardized Mortality Ratio (SMR) For Selected Causes of Death, by Birth Year

	1940-1944		1945-1946		Total	
Cause of Death	SMR	95% CI	SMR	95% CI	SMR	95% CI
Congenital Anomalies	1.27	0.87, 1.79	1.03	0.49, 1.89	1.20	0.86, 1.62
Conditions of perinatal period	1.42	1.10, 1.82	2.28	1.67, 3.05	1.69	1.39, 2.04
Congenital Anomalies and conditions of perinatal period	1.37	1.11, 1.67	1.87	1.41, 2.44	1.52	1.28, 1.78
Total Mortality	0.97	0.88, 1.07	0.99	0.83, 1.16	0.97	0.89, 1.06

To further investigate the possibility that the higher than expected mortality might be related to operations at Hanford, additional analyses were conducted according to year of death, classified as before 1945 (beginning of Hanford operations) and 1945 or later. Standardized mortality ratios were calculated for each of the ten major cause of death categories, and for each geostratum, for males and females separately, for the two date of death time periods. Table Appendix 23-8 provides the results by cause of death category. For total mortality, there was little difference in the SMRs for deaths before 1945 and for the period from 1945 on (SMR = 1.06 vs. 0.95, respectively), and neither was statistically significant. This pattern was similar in males and females, although the SMR for females was slightly higher in the earlier period (SMR = 1.14) than the later (SMR = 0.91). For congenital anomalies, the SMR for the period prior to 1945 was higher than for the period 1945+ (SMR = 1.46 vs. 0.95), and was higher for both males and females. Similarly, for conditions of the perinatal period, the SMR for the period prior to 1945 was higher than for the period 1945+ (SMR = 1.79 vs. 1.56), and was higher for females (SMR = 2.03 vs. 1.31) but not for males (1.63 vs 1.74).

Table Appendix 23-8. Standardized Mortality Ratio (SMR), by Sex, Cause of Death, and Year of Death

	Year of Death < 1945						Year of Death 1945+					
	Female		Male		Total		Female		Male		Total	
Cause of Death	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Infectious/parasitic	1.10	.23, 3.22	2.49	.999, 5.13	1.80	.87, 3.32	.12	.01, .42	.36	.19, .61	.28	.16, .46
Malignant neoplasm	10.78	.27, 59.90	0	--	4.11	.10, 22.85	1.14	.82, 1.54	.84	.56, 1.21	.99	.78, 1.25
Diabetes	28.15	.71, 156.4	0	--	18.08	.46, 100.47	.80	.16, 2.32	.76	.21, 1.95	.78	.31, 1.60
Cardiovascular disease	0	--	0	--	0	--	1.22	.70, 1.98	1.28	.91, 1.76	1.26	.95, 1.65
Pneumonia & influenza	.14	.004, .80	1.20	.60, 2.16	.75	.38, 1.30	.63	.17, 1.61	.36	.07, 1.04	.47	.19, .98
Gastrointestinal disorders	0	--	1.27	.03, 7.07	.81	.02, 4.49	0	--	1.07	.43, 2.21	.65	.26, 1.34
Complications of pregnancy	0	--	0	--	0	--	0	--	0	--	0	--
Congenital anomalies	1.71	.85, 3.05	1.32	.72, 2.21	1.46	.94, 2.16	.63	.20, 1.48	1.20	.62, 2.09	.95	.55, 1.52
Condition in perinatal period	2.03	1.36, 2.92	1.63	1.13, 2.27	1.79	1.38, 2.29	1.31	.75, 2.12	1.74	1.18, 2.49	1.56	1.14, 2.09
External Causes of Injury/Poisoning	1.06	.22, 3.10	.65	.13, 1.90	.80	.30, 1.75	1.21	.85, 1.68	1.15	.94, 1.40	1.17	.98, 1.38
All other causes	.50	.22, .99	.23	.08, .49	.33	.18, .55	.75	.45, 1.18	.71	.46, 1.05	.73	.53, .98
Total	1.14	.86, 1.48	1.01	.79, 1.26	1.06	.89, 1.26	.91	.76, 1.07	.97	.86, 1.09	.95	.86, 1.04

Table Appendix 23-9 shows the results of the year of death analyses by geostratum for those who died at under age 5. The excess mortality in the geostratum defined by births in Franklin County was concentrated in the later time period. The SMR for deaths from 1945+ was 2.91 (95% CI = 1.46-5.21), and for deaths before 1945 was 0.73 (95% CI = 0.24 – 1.71). This excess in the later time period was seen in both males and females, and to a greater extent in males. No other geostratum exhibited an appreciable difference in mortality according to year of death category.

Table Appendix 23-9. Standardized Mortality Ratio (SMR), by Sex, Geostrata, and Year of Death, for Those Who Died at Age<5

	Year of Death < 1945						Year of Death 1945+					
	Female		Male		Total		Female		Male		Total	
Geostrata	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Richland	1.45	.04, 8.04	.68	.02, 3.77	.92	.11, 3.33	.36	.07, 1.04	.69	.30, 1.35	.55	.27, .98
Pasco/Kennewick	1.56	1.01, 2.30	1.25	.85, 1.77	1.37	1.04, 1.78	.84	.38, 1.58	1.29	.79, 1.99	1.10	74, 1.59
Walla Walla City	.28	.01, 1.53	1.14	.42, 2.48	.79	.32, 1.62	.76	.16, 2.21	.53	.11, 1.56	.62	.23, 1.36
Benton County	1.38	.80, 2.21	.97	.57, 1.53	1.13	.79, 1.58	1.05	.45, 2.07	1.30	.71, 2.18	1.20	.75, 1.81
Franklin County	.74	.09, 2.69	.72	.15, 2.11	.73	.24, 1.71	1.95	.40, 5.70	3.58	1.54, 7.04	2.91	1.46, 5.21
Walla Walla County	.23	.01, 1.29	.63	.17, 1.61	.47	.15, 1.10	.44	.05, 1.58	.60	.16, 1.53	.53	.20, 1.16
Okanogan County	1.05	.13, 3.79	1.09	.23, 3.20	1.08	.35, 2.51	1.92	.52, 4.91	1.03	.21, 3.01	1.40	.56, 2.89
Ferry/Stevens Counties	1.47	.30, 4.31	1.11	.23, 3.23	1.26	.46, 2.75	1.39	.29, 4.06	.32	.01, 1.77	.75	.21, 1.93
Adams County	.79	.26, 1.85	.72	.29, 1.49	.75	.39, 1.31	0	--	.34	.01, 1.90	.20	.005, 1.09
Total	1.14	.86, 1.48	1.01	.79, 1.26	1.06	.89, 1.26	.81	.56, 1.12	1.01	.77, 1.29	.93	.75, 1.13

References

(1) Breslow NE and Day NE. Statistical Methods in Cancer Research. Lyon, France: International Agency For Research on Cancer: 1987.

(2) Wood J, Richardson D and Wing S. A simple program to create exact person-time data in cohort analyses. IJE, 1997; 26:395-99.

Recommendations From The "Review of the Hanford Thyroid Disease Study Draft Final Report" by the National Academy of Sciences Committee on an Assessment of Centers for Disease Control and Prevention Radiation Studies From DOE Contractor Sites

HTDS Study Management Team Responses

In December, 2000, the National Academy Press published a report entitled: " Review of the Hanford Thyroid Disease Study Draft Final Report". This 218-page report contained several specific recommendations (summarized in the Executive Summary of the report, pages 17-39). Each of these recommendations is listed below, with a response from the HTDS Study Management Team.

A. EPIDEMIOLOGIC AND CLINICAL METHODS AND DATA COLLECTION

A.1. An adequate review of the cytopathology results is needed.

A.1.a. Request an independent review of the FNA biopsy slides.

Response: The design of the HTDS included interpretation by a cytopathologist of all thyroid cytology specimens obtained by fine needle aspiration (FNA) biopsy of thyroid nodules. These interpretations of thyroid biopsy material were performed by a single, experienced cytopathologist in Seattle during the entire five year clinical evaluation period. During the development of the HTDS protocol, the HTDS investigators considered having a panel of cytopathologists review each set of slides for the HTDS. After considering many factors, it was decided that the consistency of the review offered by one experienced cytopathologist outweighed the possible advantages of using a panel of reviewers. After considerable peer review and approval by a federal advisory panel, this decision was adopted for the HTDS in the early 1990's.

We performed 252 FNA biopsies on individuals with thyroid nodules during the 5 year field work at various clinics throughout Washington State. All of these specimens were reviewed by the same cytopathologist. At the conclusion of the five year clinical evaluation component of the study, there were some peer reviewers who suggested that we have additional quality control assessment performed for the cytopathology results, a suggestion also transmitted by the NAS. We therefore decided to have an independent cytopathological review all 252 sets of slides.

This second review was performed by an experienced cytopathologist from the University of Washington. The results of this review showed some degree of disagreement in 32 cases for an agreement rate of 87.3% (252-32)/252 = 87.3%) for the entire cohort. None of these 32 cases involved a disagreement regarding a diagnosis of thyroid cancer. Detailed evaluation of the reviewer comments in these 32 cases showed that for only 18 cases would there be a possible change in the final diagnosis for a participant, typically involving one type of benign lesion versus another type. Thus the overall agreement with the original study cytopathologist was

92.9% or disagreement of 7.1%. While this result indicates quite good overall agreement, there still was potential disagreement in 18 cases. The HTDS study management team decided that these 18 cases should undergo further review.

A third independent cytopathological review was arranged with two cytopathologists at the University of Washington, who reviewed all 18 cases according to the following protocol:

1. All of the FNA slides for the 18 cases were provided to one of the cytopathologists who reviewed them without knowledge of the original cytology interpretation.
2. A detailed written microscopic description and diagnostic impression was recorded for each case.
3. The original cytology report was then reviewed by the cytopathologist.
4. The reviewer then recorded whether he was in agreement or disagreement with the original opinion.
5. For cases that were in disagreement, the slides were reviewed concurrently with the second cytopathologist (from the University of Washington) to reach a consensus opinion.

The results of this review showed 2 cases of disagreement and 16 cases of agreement between the third reviewer and the original study pathologist. The fourth reviewer concurred with the 2 disagreements of the third reviewer. Neither of the disagreements involved cancer versus benign cytology but rather disagreements between benign versus intermediate probability of follicular neoplasm. In both cases, chronic thyroiditis and hypothyroidism were present. In both cases, the results letter and recommendations that were initially sent to the participants during the study informed the patient that thyroid cancer was very unlikely but could not be ruled out. The results of these additional quality control procedures strengthens the validity of the approach in the original study design of having a single, experienced cytopathologist review all of the FNA specimens.

A.1.b. Request clarification of certain hypocellular specimens with abundant colloid that were classified as benign.

Response: The NAS report (page 54) recommends that additional attention be given to FNA specimens that were classified as benign due to abundant colloid but were acellular or hypocellular. First, hypocellular cases were classified as nondiagnostic unless abundant colloid was demonstrated. If abundant colloid was demonstrated it was thought these were highly likely to be benign lesions in part because the HTDS thyroid examiner team obtained more extensive FNA material than is customary in clinical practice (typically 4-10 aspirations per nodule, providing 10-20 slides of specimen material to the cytopathologist). In addition, during an extensive cytopathology review by 2-3 independent cytopathologists (see above), no case involving abundant colloid with a hypocellular specimen was interpreted to be suspicious or suggestive of malignancy. It is therefore quite unlikely that this category of benign nodules included any thyroid cancer cases. However, it is acknowledged that a hypocellular specimen with abundant colloid cannot entirely rule out a malignancy. While repeat FNA material on these cases is not available, we did perform a separate dose-response analysis excluding all such cases with abundant colloid with hypocellular specimens from the benign category with no change in the results (see Results IX-D.2.c.4).

A.1.c. Clarify the criteria for an adequate biopsy.

Response: The NAS report requests HTDS criteria on adequacy of biopsies in terms of numbers of cells and preparation technique. While there are no clear-cut universal criteria on these issues, it is generally recommended that 6-8 slides of material be available for review. The HTDS study physicians produced on average double this amount and often triple this number of slides for microscopic review. With regard to number of cells, the criteria for adequacy used by the HTDS cytopathologist were consistent with that in clinical practice requiring multiple clusters of thyroid cells (usually greater than 6) on multiple slides.

A.2. The HTDS investigators should indicate for how many potential past thyroid diagnoses they were unable to obtain any medical confirmation, with a breakdown by reported type of thyroid disease and dose.

Response: This NAS recommendation seems to stem from a discussion in the body of the text of the NAS Review (Executive Summary, page 56) which states that "the investigators reported that 37% of the 1264 medical records they sought could not be obtained. (The actual number is 1259 after excluding the requests for an ineligible subject, although a more appropriate number to examine is the 1317 medical records and slides requested). It would be desirable for them to indicate for how many potential thyroid diagnoses they were unable to obtain any medical confirmation, preferably with a breakdown by reported type of thyroid disease". The concern here appears to suggest that for the individuals where medical records could not be obtained, thyroid diagnoses were potentially missed and not included in the HTDS results. However, for all evaluable participants, current diagnostic information at the time of clinic evaluation served as the primary basis for thyroid diagnosis (the basis with highest degree of validity). Thus, even if a medical record could not be obtained, the likelihood of a missed diagnosis is generally low. This is because in most situations the HTDS evaluation will provide valid data regarding whether the diagnosis for which the medical record was sought, is confirmed or not confirmed. For example, in a person reporting a thyroid nodule 30 years ago, the diagnosis will be confirmed by HTDS physicians based on current physical exam and ultrasound scans. An exception would be for a person reporting thyroid cancer, who then had thyroid surgery, and then had missing medical records. However, this occurred in only one individual**.** In addition, the 37% represents the percentage of medical records requested but not received, not the number of participants for whom no medical records requested were obtained. Thus, the 37% figure quoted above by NAS greatly overestimates the possibility that those missing medical records contributed to a missing diagnosis. In order to further clarify this issue, we have added a more detailed description to section V.I.4 and V.I.5 pertaining to the diagnoses for participants with at least one missing medical record or slide.

A.3. The mortality experience should be tabulated in more detail.

Response: The HTDS was not designed to evaluate mortality, and the analyses conducted were never intended to investigate a relationship between Hanford radiation dose and cause of death among those in the cohort who died. Nevertheless, in response to a number of comments and suggestions received after the release of the Draft Final Report, including those from the NAS committee, the mortality analyses were extended to provide additional detail. The analytic methods used and the full set of findings are presented and discussed in considerably more detail in Appendix 23, and in the Discussion (section X.C.1) of the HTDS Final Report.

B. DOSIMETRY

B.1. A single document describing clearly the HEDR dose-assessment methodology, including uncertainties and its implementation by HTDS should be prepared.

Response: The models and computer programs developed by the HEDR Project are described in a series of papers and technical reports published by the HEDR investigators. It is outside the scope of the HTDS to rewrite these, which are the product of a separate research project, into a single document. Additional detail is provided in Section VI of the HTDS Final Report to describe the approach taken in the HTDS to use the computer programs developed by the HEDR Project to estimate individual thyroid radiation dose for study participants.

B.2. Errors in the dose-estimation model should be corrected.

Response: Revisions made to the HEDR model, computer programs, and input data following the NAS review are described in a technical report prepared by investigators from Battelle Pacific Northwest Laboratories, which is included as Appendix 22 in the HTDS Final Report (Napier B, Eslinger P, Ramsdell JV, Hope L. Responses to National Academy of Sciences Review Comments on Dosimetry in the Fred Hutchinson Cancer Research Center's Hanford Thyroid Disease Study. Battelle Pacific Northwest Laboratories, PNWD-3060, 2000.)

B.3. All dose-related uncertainties should be taken into account.

Response: As described in the technical report mentioned above (Napier B, Eslinger P, Ramsdell JV, Hope L. Responses to National Academy of Sciences Review Comments on Dosimetry in the Fred Hutchinson Cancer Research Center's Hanford Thyroid Disease Study. Battelle Pacific Northwest Laboratories, PNWD-3060, 2000; see Appendix 22 of the HTDS Final Report), two modifications were made to the CIDER program regarding uncertainty of dose estimates. The first modification added an option to randomly permute the values of dose conversion factors (DCFs), thereby eliminating an artificial correlation among dose realizations. The second modification allowed the assignment of uncertainty to dietary input values that were specified for participants whose doses were based on CATI data. These two modifications required relatively modest revision of the CIDER code by Battelle investigators, because the original version of CIDER was designed to account for uncertainty of DCFs (which were treated as uncertain for all dose calculations) and dietary intakes (which were treated as uncertain when values are not specified). Accounting for other sources of uncertainty, such as errors in residence histories, sources of food, milk and milk products, and lifestyle specifications would require major revision of the CIDER code, since it contained no provision for uncertainty of these inputs. This was outside the scope of HTDS and was not undertaken as part of the revision of the CIDER program.

Incorporating uncertainties on dietary data reported by CATI respondents had relatively little impact on the dose estimates of the 1979 living evaluable in-area participants whose doses were based on CATI data, or on the estimated uncertainties of those doses. For example, a set of dose estimates for these 1979 participants was calculated using reference diet uncertainties with scale factors SF = 1 (the maximum value allowed in the modified version of CIDER) and $SF_0 = 0.25$. As described in section 7.3 of Appendix 22 of the HTDS Final Report, this applied uncertainties proportional to those of the HEDR default dietary values when consumption values greater than 0

were reported by the CATI respondent. When the CATI respondent reported no consumption, uncertainties of the same relative magnitudes were applied to the 0.25 times the mean of the HEDR default values. These new dose estimates were on average only about 3% larger than the original primary dose estimates that were calculated with no uncertainty applied to dietary input data from CATI. The ratios of the 95th percentile doses to the medians, which provide a measure of the uncertainty of the dose estimates (see section VIII.B.3.a of the Final Report) also increased an average of 3% larger when uncertainty was incorporated in the CATI dietary input data, although the geometric standard deviations (GSDs) increased an average of only 0.8%. In view of the small changes produced by incorporating this additional component of uncertainty, further analyses using these dose estimates were not pursued.

C. STATISTICAL ANALYSES

C.1. A number of key tables should be included in the final report to help readers to interpret the dose-response results.

Response: Tables showing the numbers and percentages of participants with disease and thyroid UDA outcomes have been integrated into the sections for each outcome, rather than gathered into an appendix as they were in the draft Final Report. Note that these tables address the apparent intent of the suggestion to "[expand] the tables of high- versus low-dose results" (page 87 of the NAS Report). The tables presenting "high- versus low-dose results", which are not based on estimated dose categories, provided the kind of "additional set of confirmatory analyses" that the reviewers requested (page 88 of the NAS Report). The dichotomous exposure variable -- relatively high versus low exposure -- is defined in section VIII.B.3.b.2 of the Final Report. Analyses of outcomes in relation to this dichotomous exposure variable, including tables of numbers and percentages of participants with disease and thyroid UDA outcomes, have been integrated into the sections for each outcome, rather than gathered into a single section as in the draft Final Report. A number of other additional tables and figures have been added to the Final Report.

C.2. The HTDS investigators should report on those who were out of the dosimetry area for part of the exposure period and examine the impact of the assumption of zero dose received during such periods.

Response: The NAS Committee was incorrect to state that HTDS assumed that participants received "zero dose" while outside the "dosimetry area", i.e., the approximately 75,000 square mile geographical domain that was defined as part of the HEDR Project (see Figure II.A-1). It is evident from the HEDR results that people living outside the domain could have been exposed to ^{131}I from Hanford. Therefore as noted in section VIII.C.1.a.3 of the Final Report, it was not assumed that participants received "zero dose" while outside that area. As described in Section IX.B of the Final Report, the CIDER program, which was developed by the HEDR Project and used by the HTDS, only calculated thyroid doses received while participants were living within that geographical domain. The boundaries of that domain were defined as part of the HEDR Project based on two considerations: the decreasing reliability of the HEDR model for atmospheric transport and deposition of radionuclides at increasing distances from Hanford, and the likelihood that doses received outside the domain were low. Since the CIDER program did not calculate thyroid doses received while participants lived outside the HEDR geographical domain, only very crude representations of those exposures were possible. Therefore only very

limited scoping analyses of the possible effects of including such exposures were appropriate for the HTDS. The scoping analyses that were performed are described in section VIII.C.1.a.3 of the Final Report, and the results of these analyses are described in the subsections entitled "Scoping Analyses Regarding Out-of-Area Participants" in sections IX.C through IX.Q of the Final Report. These analyses addressed the impact of excluding the 249 living evaluable out-of-area participants (i.e., those who never lived within the HEDR domain between December 1944 and the end of 1957).

The proportion of the 3191 living evaluable in area participants who were outside the HEDR domain varied virtually on a day-by-day basis, but in general increased with the passage of time, reflecting the accumulated effect of participant's families that permanently moved out of the area. Thus on January 1, 1945, a total of 147 living evaluable in area participants were outside the HEDR domain. These accounted for 4.6% of the 3191 living evaluable in area participants (although 967 of these 3191 were born after January 1, 1945). On January 1 of 1946, 1947, and 1948, this increased to 435 (13.6%, with 362 not yet born), 576 (18.1%) and 616 (19.3%), respectively. Due to the complexity of the dosimetry system and its inability to provide anything more than crude approximate dose estimates for scoping analyses, no attempt was made to estimate doses received while the "partial out-of-area" participants were outside the HEDR domain.

If in area participants who had a particular disease or thyroid UDA outcome were more (or less) likely to be in the "partial out-of-area" group, or were more likely to receive higher (or lower) thyroid doses from Hanford's ^{131}I while living outside the HEDR domain, compared to those without the disease or UDA outcome, then CIDER's inability to estimate doses received outside the HEDR domain might bias the estimated dose response for that outcome. In particular such a differential or outcome-related underestimation of actual thyroid doses would tend to reduce an apparent dose response if participants with the outcome tended to receive higher doses while outside the domain. This is because the actual total thyroid doses from Hanford's ^{131}I for participants with the outcome would tend to be underestimated to a greater degree than those of participants without the outcome. However it is very unlikely that decisions made in the 1940s or 1950s to move to a new location which happened to be outside the HEDR domain are related to a child's subsequent development of a disease outcome, nearly all of which were diagnosed much later in life, or to a thyroid UDA observed at the HTDS clinic. Therefore it is unlikely that CIDER's inability to estimate doses received outside the HEDR domain caused HTDS to underestimate the magnitudes of positive dose-responses.

If, as seems much more likely, the magnitudes of the doses received by the "partial out-of-area" participants while outside the HEDR domain were unrelated to disease and thyroid UDA outcomes, then the effect of omitting those doses would be to increase the apparent magnitude of any positive dose-response, since a fixed number of excess cases caused by the actual doses received both in- and out-of-area would be attributed to the smaller doses participants received while inside the HEDR domain. Therefore, CIDER's inability to estimate doses received outside the HEDR domain was likely to cause overestimation of positive dose-responses. Consequently it is unlikely to have caused the HTDS to fail to detect dose-related increases in disease or thyroid UDA outcomes.

C.3. Analyses designed to control for possible confounding by geographic area should be conducted.

Response: The analyses described in the subsections entitled "Effect of Excluding Okanogan and Ferry/Stevens Geostrata" in sections IX.C through IX.P of the Final Report provide more meaningful and directly interpretable results concerning the impact of disease and UDA rate variations between geostrata than the stratified analysis suggested by the Committee. As described in those sections, the slopes of the sex-stratified linear dose-response models are generally increased somewhat by exclusion of the Okanogan and Ferry/Stevens geostrata, as expected since participants in those two geostrata tended to have lower estimated thyroid doses from Hanford's ^{131}I, but somewhat higher outcome rates, compared to the remaining geostrata. However for none of the disease and thyroid UDA outcomes analyzed was a statistically significant dose response observed in these analyses.

C.4. There should be a more thorough set of analyses of thyroid-disease rates by milk-drinking information.

Section IX.A.6 of the HTDS Final Report contains descriptions of dietary consumption levels reported for study participants whose doses were based on CATI data. Section IX.B.3 presents results demonstrating how estimated doses varied in relation to those dietary consumption levels, including consumption of fresh milk and milk products. As expected, since thyroid doses from Hanford's atmospheric releases of ^{131}I depend heavily on location in addition to dietary factors, the correlations between dose and milk consumption are modest (see Table IX.B-12 of the Final Report). Since these correlations were modest, and since individual milk consumption data were available only for the 1979 living evaluable participants whose doses were based on CATI data, no analyses of outcomes in relation to milk consumption were performed. Instead, relatively high and low exposure categories were defined on the basis of both milk consumption and residence history as defined in section VIII.B.3.b.2 of the Final Report (see the subsections entitled "Analysis by Dichotomous Exposure Variable" in sections IX.C through IX.P of the Final Report).

C.5. Confidence intervals should be given and used in the interpretation of the study results.

Response: Confidence intervals have been added throughout sections IX.C to IX.Q of the Final Report.

C.6. The confidence intervals should take into account all the sources of uncertainty in the dose estimates.

Response: Please see the response to the comment that "All dose-related uncertainties should be taken into account" above.

D. STATISTICAL POWER AND INTERPRETATION OF THE STUDY

D.1. The HTDS investigators should describe the sources of uncertainty in as quantitative terms as possible and interpret their results in the light of these uncertainties.

Response: The most useful description of the sources of uncertainty in the dose estimates can be found in the publications and technical reports describing the HEDR dosimetry model. The approaches taken to handling dose uncertainties in the HTDS are described in section VIII.C.2.c of the Final Report, and the results of these analyses are presented in the subsections entitled "Uncertainty" in sections IX.C through IX.Q. The impact of dose uncertainties on the study's statistical power is described in section IX.B.4 and discussed in section X.C.5 of the Final Report.

D.2. The HTDS investigators should recalculate the statistical power of the study, taking into account the dose uncertainties if this proves feasible.

Response: The description of the study's power is provided in section IX.B.4 of the Final Report.

D.3. The compatibility of the HTDS study with other studies of radiation and thyroid disease should be re-examined, taking into account the impact of dose uncertainties.

Response: The comparison of the HTDS results to those of other studies of radiation and thyroid disease is discussed in section X.D of the Final Report.

E. COMMUNICATION OF THE STUDY RESULTS TO THE PUBLIC

E.1. Delivering an unpopular message requires sensitivity to the audience's health concerns and fears. In communications about the HTDS final report, implications for individuals and families that have suffered because of thyroid disease should be carefully explained. If there are plausible alternative interpretations of the results, they should be acknowledged.

E.2. The subcommittee supports CDC's open-communication policy and strongly recommends that it continue. It recommends that a new communication plan be devised for the release of the final HTDS report and accompanying public documents, taking into account the problems that have already been encountered.

E.3. In the HTDS final report and all public documents, any significant changes made from the Draft Final Report should be clearly outlined and explained, and all remaining uncertainties should be noted and explained.

E.4. Careful consideration should be given to how to release controversial reports to the public more effectively. The subcommittee suggests that CDC convene a workshop to discuss this and other communication issues of concern.

Response: The staff of the Radiation Studies Branch of the Centers for Disease Control and Prevention (CDC) will have a summary of responses to these recommendations regarding communication of findings to the public on the CDC web site along with the study report: (http://www.cdc.gov/nceh/radiation/hanford).

Responses to Comments Received from the Public and Members of the Scientific Community.

The HTDS Study Management Team and the CDC received numerous comments from members of the public and the scientific community regarding the HTDS Draft Final Report. Comments were received through the CDC Web site, e-mail, letters and at public meetings. This appendix provides a listing of all of the comments received, along with responses to these comments from the HTDS Study Management Team. Included in the comment list are all comments received by the CDC through the end of the official comment period (July 1, 1999), as well as review comments received from a panel of independent scientists convened by the CDC to review the Draft Final Report. The comments and their responses are grouped according to general topic area. When more than one comment addresses the same question or issue, each such comment is listed and one response is provided. Otherwise, responses are provided for individual comments. Note that page or section numbers mentioned in the comments refer to the Draft Final Report; section numbers mentioned in the responses to comments refer to the Final Report.

I. DOSE ESTIMATION

I.A. HEDR and CIDER

I.A.1 *The HEDR project estimates of the amounts of ^{131}I processed and released in 1959 and 1960 are substantially less than the amounts reported by Warren (1961), which are the source of HEDR release estimates.*

I.A.2 *The HEDR project documents use Warren (1961) as a source but do not evaluate the credibility of his values; for example, he projected an unrealistically high scrubber efficiency.*

I.A.3 *The HEDR project misapplied measured release-factor data from 1959-1960 to the period 1951-1957, when less emission-control equipment was in place.*

I.A.4 *The HEDR project incorrectly accounted for operation of the silver reactors in the B and T plants by inexperienced personnel during the first 18 months after installation in 1951.*

I.A.5 *The HEDR project substantially underestimated the source-term uncertainties for the B, T, and REDOX plants.*

I.A.6 *The HEDR project inadvertently used the medians instead of the arithmetic means of the monthly source terms for the air-concentration and ground-deposition calculations.*

I.A.7 *The HEDR project did not propagate the source-term uncertainties to air concentrations, ground deposition, and doses.*

I.A.8 *The air pathway doesn't account for the topography of the region.*

I.A.9 *The HEDR model doesn't account for changes in rates of release.*

I.A.10 The HEDR model doesn't account for chemical effects of the atmosphere (speciation).

I.A.11 There are other models that are better and that have been tested.

I.A.12 "Researchers didn't know the truth about Hanford's reactor fires and what was actually released."

Response: These comments are directed at the dose estimation system, which was developed by the Hanford Environmental Dose Reconstruction (HEDR) project. The dose estimates calculated using the HEDR system are very useful for the purposes of an epidemiological study such as the HTDS. Therefore, they were used for the primary analyses of the associations between outcomes and exposure, as described in section VIII.C.1. However additional analyses using alternative representations of exposure were also included in order to reduce the study's reliance on HEDR dose estimates (see Section VIII.B.3.b and the subsections entitled "Analysis … in Relation to Alternate Representations of Exposure" in sections IX.C through IX.P of the Final Report).

I.A.13 It is not clear whether the soil deposition estimates were based on meteorological data from 1944-47 or from the 1980s (page 4, Section IV, Study Design).

Response: In the final HEDR model, atmospheric deposition of ^{131}I from Hanford was based on meteorological data from 1944-49 (1). See also the HEDR reports by Ramsdell et al. (2) and Stage et al. (3). No revisions in this regard were made in the Final Report.

I.B Other issues concerning dose estimation

I.B.1 All the animals and crops were also affected. A lot of those crops, particularly alfalfa, were marketed in western Washington State. This alfalfa fed the dairy herds of western Washington and probably contaminated all milk products.

Response: The HEDR system only provides estimates of the thyroid radiation doses people received while living within the 75,000 square mile region in eastern Washington State and adjacent areas of Oregon and Idaho (the "HEDR domain"), shown in Figure II.A-1 of the Final Report. It does not provide estimates of doses that people could have received while living in western Washington State or elsewhere outside this HEDR region. Therefore only limited scoping analyses of the impact of possible exposures received while study participants lived outside the HEDR domain were possible. These scoping analyses are described in section VIII.C.1.a.3 of the Final Report, and the results are described in the subsections entitled "Scoping Analyses Regarding Out-of-Area Participants" in sections IX.C through IX.P of the Final Report.

I.B.2 NTS doses for Stevens, Ferry, Okanogan counties are generally higher than for Benton, Franklin and Adams counties. Perhaps more significantly, the GSD is much higher for Stevens, Ferry, Okanogan counties. It would be useful to include a section that describes how these higher NTS exposures in the HEDR low-dose counties were taken into account and why they were not considered to have constituted a confounding factor.

I.B.3 P. 90 The authors indicated in Section E.3.c. that doses from the Nevada Test Site were calculated for the study subjects. There will be some reviewers who will argue that these doses should have been added to the Hanford doses and incorporated into the final dose response analysis. This issue is addressed in Section VII.D, but it needs to be discussed here, too, or the later section where it is discussed should be referenced here.

Response: In the design and analysis of HTDS, no assumption was made about whether exposure to NTS fallout either was or was not a confounding factor; instead this question was examined in the analysis of the study's results. The rationale for not adding Hanford and NTS doses to produce a total dose is explained in section VIII.D.1 of the Final Report. The calculation of estimated NTS doses, and their analysis as a potential confounding factor or effect modifier, is described in section VIII.D of the Final Report. The results of these analyses are given in the sections entitled "Confounding and Effect Modification" in sections IX.C through IX.P of the Final Report. As described in those sections (and summarized in Section X.C.4), for none of the disease and thyroid UDA outcomes was estimated thyroid dose from the NTS identified as a confounding factor or effect modifier.

I.B.4 Because of including Richland residents (see the previous comment), the HTDS analysis could have been confounded by a significant contribution from the inhalation pathway. It is my understanding that HEDR did not estimate a source term for methyl iodine. It would be useful if the final report included a discussion of this factor.

Response: The HTDS analysis was not confounded by the dose contribution from the inhalation pathway because the inhalation doses are included in the dose estimates calculated by the CIDER program. As illustrated by representative dose calculations in Table 4.4 and Figure 4.18 of the summary HEDR report concerning the atmospheric pathway (4), the estimated inhalation doses were not trivial, ranging up to 21 mGy in 1945 for representative individuals less than 1 year old living immediately east of the Hanford site (up to about 10 mGy for Richland).

The HEDR model assumed that the iodine was in the elemental form at the time of its release during the chemical dissolution processes at Hanford, and was then partitioned between elemental, organic, and particulate forms (5). The organic forms included methyl iodide (CH_3I).

I.B.5 I wonder why someone born at ground zero, like me would fit the same scale as if born at your test area's edge.

Response: It's unclear what is meant by "fitting the same scale" in this comment. However, it should be noted that the HTDS examined the relationship of disease risk and estimated radiation dose to the thyroid. The study was designed to include people with a wide range of doses, from extremely low to the highest doses. Therefore the cohort included, among others, persons who

likely to have lived in early childhood in the downwind counties nearest to Hanford: Benton, Franklin, and Adams. These counties may include the "ground zero" mentioned in the comment.

I.B.6 I don't think the study is accurate because people moved all over.

Response: The fact that people have moved over the decades from the 1940s until the 1990s was dealt with in the design of the HTDS in the following ways.

Definition of the cohort. Many people who were exposed to the ^{131}I from Hanford no longer live near Hanford, or even in the Pacific Northwest. To ensure that the study participants would be as representative as possible of the population of interest, the cohort was defined on the basis of characteristics at birth (birth date and mother's usual place of residence from birth records) without regard to subsequent movement to other locations (section IV.A.1 of the Final Report). Their subsequent movements or "residence history" were then taken into account in estimating their radiation doses, as described below.

Locating and recruiting study participants. The difficulty of locating and recruiting potential study participants was likely to be greater for those who have moved away from the Hanford area. However uniformly extensive efforts were made to trace, locate and recruit every selected person, regardless of current location of residence. This is described in sections V.B and V.C of the Final Report.

Participation in study clinics. To increase the chances that potential participants could attend study clinics regardless of their current place of residence, the study helped to arrange transportation and paid travel costs as described in section V.E.3 of the Final Report.

Estimating radiation doses from Hanford's ^{131}I. In the HTDS, the primary representation of participants' exposures to ^{131}I from Hanford was the estimated thyroid dose calculated using the system developed by the HEDR project. Each participant's individualized dose estimate was calculated using specific information provided by the participant or his/her CATI respondent. The information used to calculate estimated doses included the participant's "residence history", i.e., the locations where he/she lived and the times he/she lived in each location.

Out-of-area participants. The HEDR system only provides estimates of the thyroid radiation doses people received while living within the 75,000 square mile region in eastern Washington State and adjacent areas of Oregon and Idaho, shown in Figure II.A-1 of the Final Report. Some study participants (designated "out-of-area" participants) never lived in this region between mid-December 1945 and the end of 1957, and for such participants, the HEDR system cannot calculate a dose estimate. Since it was quite possible that the out-of-area participants could have been exposed to ^{131}I from Hanford, scoping analyses were performed to assess the impact of their exclusion from the dose-response analyses (see section VIII.C.1.a.3 of the Final Report and the subsections entitled "Scoping Analyses Regarding Out-of-Area Participants" in sections IX.C through IX.P of the Final Report).

Estimating doses from the Nevada Test Site. The release in 1997 of information concerning exposures to radioactive fallout from the NTS provided an opportunity to include some information about these exposures in the analysis of HTDS results. In particular, estimated thyroid doses from NTS fallout were calculated for HTDS participants as described in sections

VI.C and VIII.D of the Final Report. These estimated doses accounted for changes in the participants' places of residence, whether inside or outside the HEDR region.

I.B.7 Many aspects of the study were based on criteria from the Hanford Environmental Dose Reconstruction project which is flawed. For example that study computed the radiation amount from butter using its half life. This is very short sighted of them considering rural eastern Washington (state) farms did not have electricity in the forties. How could home made butter possibly be edible in August of 1945 if kept un-refrigerated for that time period?

Response: The CATI included questions regarding the quantities of raw cow's and goat's milk and milk products (cream, butter, buttermilk, cottage cheese, yogurt, and ice cream combined) consumed by the participant. Thus the CATI respondents were able to report whether or not the participant consumed raw milk products, including butter. These questions were also asked regarding the participant's mother's diet if she was pregnant with or breastfed the participant after December 1944. Of course this kind of detailed information was not available from the Expanded In-Person Interview used for participants without CATI respondents. It should also be noted that additional analyses using alternative representations of exposure were also included in order to reduce the study's reliance on HEDR dose estimates (see section VIII.B.3.b and the subsections entitled "Analysis … in Relation to Alternate Representations of Exposure" in sections IX.C through IX.P of the Final Report).

I.B.8 Suggest doses be given for dichotomous exposure classification. Suggest that categorical analysis should be included in the report.

Response: Two sets of analyses using categorical exposure classifications rather than dose estimates were performed. As described in section VIII.B.3.b of the Final Report, the first of these was based simply on geostrata, and the second on a dichotomous variable accounting for participants' residence histories and milk consumption histories. Distributions of estimated doses are shown by geostratum in Table IX.B-4 and by the dichotomous exposure variable in Table IX.B-13 (section IX.B.3 of the Final Report). Results of analyzing disease and thyroid UDA outcomes in relation to these categorical exposure classifications are described in the sections entitled "Analyses … in Relation to Alternative Representations of Exposure" in sections IX.C through IX.P of the Final Report.

I.B.9 There should be clearer explanation of why age adjustment was done in dichotomous exposure analysis, and not elsewhere.

Response: As described in section VIII.C.2.a.2 of the Final Report, analyses of disease and thyroid UDA outcomes in relation the categorical alternative representations of exposure, i.e., geostratum and the dichotomous exposure variable, were adjusted for a possible effect of age at the time of HTDS examination. This was done because there were small differences in the distributions of age at examination among the geostrata and between the high and low exposure categories (see section IX.A.7 of the Final Report). Note that in the primary analyses of dose responses for disease and thyroid UDA outcomes, the possibility of confounding by age at examination was addressed by the age-adjusted analyses describe in the subsections entitled "Confounding and Effect Modification" in sections IX.C through IX.P of the Final Report.

I.B.10 Did the study consider the possibility that milk, originating near Hanford, was sent to Spokane and therefore consumers in Spokane were at high risk? And "shouldn't this assumption have driven a more exhaustive search in the Spokane region?"

Response: The distribution of commercial milk and milk products throughout the HEDR geographical domain was modeled from a variety of sources of information as part of the HEDR project (6). Estimates of doses received by study participants while living in Spokane (or anywhere else in the domain) took this information about milk distribution into account. Regarding the question about a "more exhaustive search in the Spokane region", we assume this refers to the selection of Benton, Franklin, Adams, and Walla Walla counties as the geostrata for identification of persons likely to have high exposures. As described in Section IV.A.1 of the Final Report, these areas were chosen because the Phase I and final HEDR results indicated that locating people who lived as infants and young children in these counties during the earliest years of Hanford operations provided the best chance of including as many highly exposed participants as practically possible. This was based on the evidence that, while residents of Spokane were indeed exposed to ^{131}I from Hanford, they were likely to have received lower doses than people who lived in the late 1940s in the selected counties.

I.B.11 The HEDR project included both airborne releases of iodine 131 and exposures related to the Columbia River. The HTDS only included exposures to airborne iodine 131. A discussion of this exposure pathway might help the reader assess the importance of omitting this potential exposure from consideration in calculating doses. Additionally, given that you did not include potential exposures associated with the Columbia River, we think that you need to be clearer that you are assessing only exposures related to airborne releases of iodine 131.

I.B.12 HEDR [needs to] to acknowledge that documentation from de-classified documents... ...over the last several years have shown that releases to the river in the '50s were as much as 50% higher than the HEDR study shows.

Response: The HEDR model for exposures related to the Columbia River did not include ^{131}I or any other radioisotopes of iodine (7; 8). Explicit description of the ^{131}I from airborne releases has been added at various places in the Final Report.

I.B.13 (P.87 of draft report) The study uses the information from the study subject about water source to determine whether or not pasture used by the appropriate milk cows was irrigated or not. What is the basis for using this indirect information in this manner? What would have been the impact on dose of misclassifying the cow's source of pasture?

Response: The final HEDR model included several feeding regimes for cattle and goats, to account for the various ways that those animals might be fed as determined by the seasonal availability of various kinds of feed, e.g., fresh pasture grass, green chop, stored feed for cattle. In order to estimate the thyroid radiation dose of a person who consumed raw cow's or goat's milk or milk products, feeding regime(s) had to be specified for the animals in question. The CATI provided an opportunity to try to identify the most appropriate feeding regimes of family cows for participants with CATI respondents (HEDR-specified default feeding regimes were used for participants without CATI dosimetry data). However the CATI was developed and in use for data collection in November 1992, well before the final specifications of the HEDR models for

estimating thyroid radiation doses were known. Therefore, as described in section VI.A.3.a of the Final Report, data that were available from the CATI were used to impute the feeding regime: the main source of water for family cows, and the percentage of feed that was pasture, green chop, or other fresh greens. These two items, along with the location of residence, were used to impute the cow feeding regime. No additional analyses were performed to assess the impact of this issue on dose estimates.

I.B.14 P. 87 The authors state that in April 1996 they brought to the attention of the HEDR Task Completion Working Group and others the issue of inconsistencies in dairies between the HEDR data and the study subjects. Has there been a resolution of this issue at this time? How did HTDS handle this issue in the dose calculations? What impact does this issue have on the dose estimates?

Response: There were two possible reasons for these discrepancies: 1) the HEDR project might have found no evidence of a dairy's operation or supply to the area in question during the period in question (see Deonigi, et al, [9]) for a description of the HEDR commercial milk distribution model); or 2) the CATI respondent may have misidentified a dairy. The majority of these discrepancies were unique, i.e., they occurred only once in all of the CATI interviews performed for HTDS. As noted in section VI.A.3.a of the Final Report there were only 12 instances in which the same discrepancy was found in CATIs of more than one respondent. In eight of these 12, the dairy in question was mentioned by only two CATI respondents. Since the reported discrepancies did not provide definitive evidence of inadequacies in the HEDR commercial milk distribution model, that model was not revised in response to these discrepancies. Therefore HTDS adopted the following approach. Whenever a CATI respondent indicated that the participant consumed milk or milk products from a dairy that did not, according to the HEDR data, serve the area in question during the period in question, the dairy was specified as "unknown" in the scenario file of input data for the participant's dose calculation. This had the effect of assigning the HEDR location- and time-specific default as the source of commercial milk and milk products. If the HEDR model specified that only a single dairy served the location at that time, then that dairy was assumed to be the source of dairy products. If the HEDR model identified two or more dairies that served a region during the time period of interest, then the default was defined as a mixture of milk and milk products from those dairies.

In order to assess the impact of this issue on the dose estimates, it would be necessary to modify the commercial milk distribution model built into the HEDR model. However, because the HEDR project found no evidence that the dairies in question served the specific areas during the time periods in question, no information is available regarding the amounts, and in some cases the sources, of milk and milk products they supplied. Therefore any such modifications would require assumptions about quantities for which there is no direct evidence. Consequently no additional analyses were performed to assess the impact of this issue on dose estimates.

I.B.15 P. 88 The authors state that "…it was impractical to allow a participant's reference diet category to change over time." What was the impact of this computer code limitation on the calculated doses, and thus the dose response analysis?

Response: Reference diet libraries are used by the HEDR model to provide dietary intake values, i.e., quantities of food and milk consumed, when those values are not specified in a participant's scenario file of CIDER input data (see section VI.A.3.a of the Final Report). Since it was impractical to allow participants' reference diets to change over time, it was not possible to assess

directly the impact of this limitation of the estimated doses or dose-response results. However, as described in section IX.B.1 of the Final Report, two alternative sets of dose estimates were calculated. These differed from the primary dose estimates either by replacing the participant-specific information obtained from CATIs with HEDR data (first alternative), or by replacing the HEDR default milk consumption data, when required, defaults derived from the HTDS CATI data (second alternative). The dose-responses for disease and thyroid UDA outcomes were analyzed using the primary and two alternative sets of dose estimates. As shown in the subsections entitled "Analysis … in Relation to Alternative Dose Estimates" in sections IX.C through IX.M, IX.O, and IX.P of the Final Report, for neither alternative set of doses were the study's findings changed. In addition, the source of dosimetry data (CATI versus Expanded In-Person Interview) was treated as a potential confounding or effect modifying factor. Since the CATIs provided specific dietary intake values for most participants with CATI data, while no specific dietary data were obtained from the Expanded In-Person Interviews, this analysis reflected in part the effect of the selection of the backyard cow's milk reference diet library. No further analyses were conducted to investigate the impact of the limitation to a single reference diet.

I.B.16 What is the impact on the dose estimates of using "fuzzy date codes" for residences, and how did you evaluate this impact?

Response: The "fuzzy date codes" were a set of conventions that were used when CATI respondents or study participants were unable to provide exact dates for events such as changes in residence or dietary practices. For example, if an interviewee could only specify the month within which an event occurred, the event was assumed to have occurred on the 15th of that month. If only the year was known, then the event was assumed to have occurred on July 1 of that year. The following dates were used if only the season of the year was known: February 1 for Winter, May 1 for Spring, August 1 for Summer, and November 1 for Autumn.

The CIDER program required specification of exact dates in each participant's scenario file, making it impractical to investigate the impact of uncertainties in event dates. Therefore the potential impact of this on the estimated dose responses was not investigated.

I.B.17 Consistency among individuals' dose estimates is lost when each individual's dose is represented by the median estimate.

I.B.18 The final report should include a discussion that addresses why the loss of correlation (among the CIDER realizations) was not considered to be a problem when most of the dose-response analyses relied on only one value of each participant's dose estimates (i.e., the median).

I.B.19 Question the loss of correlation because each person's median dose comes from a different [could not read].

I.B.20 Is it true that higher and lower estimated doses were actually higher and lower median doses? And that most of the dose response analysis in the study is based upon median values?

Response: The primary descriptive and inferential analyses using individual dose estimates were based on the median of each living evaluable in-area participant's 100 dose realizations

calculated by the CIDER program; see section VIII.B.3.a of the Final Report. The statement in the first comment above is true, and it is also true for the two other point estimates of dose in section VIII.B.3.a of the Final Report, the geometric and arithmetic mean doses. However the practical value of having a single point estimate of dose for both descriptive purposes and analyses of the magnitude of exposure and dose-response relationships far outweighs this criticism. The second comment is incorrect in its assumption that "loss of correlation" arising from the use of medians was not considered a "problem". As just mentioned, estimated dose-responses based on the medians are of immense practical value. In addition, sections IX.C through IX.M, and IX.O and IX.P provide results estimates of the slope of the dose-response parameter for each of the sets of 100 realizations produced by the CIDER model (see the figures entitled "Plot of Estimated Slope by Dose Realization).

I.B.21 If 2/3 of the people had some type of thyroid malfunction then [speaker] would have liked to see a birth date quantity chart in the report, so he'd know who was born when, and a map that could easily tell where the doses fell.

Response: Birth years of the 3440 living evaluable study participants are tabulated in Table IX.A-1 in section IX.A of the Final Report. Maps illustrating the areas in which participants were likely to receive comparatively high or low exposures have been published by the HEDR project (7, 4). An example of such a map is shown in Figure IV.A-1 of section IV.A in the Final Report. However, it must be understood that such maps, while useful for descriptive purposes, do not accurately reflect the doses actually received by all study participants, since they do not account for participants' individual residence histories and dietary histories. The dose estimates used in the HTDS used such individual information to the extent it was available. Average estimated thyroid doses from Hanford ^{131}I are shown by sex, birth year, and geostratum in Figure IX.B-5 in section IX.B.3 of the Final Report. The cumulative incidence of disease outcomes and prevalence of thyroid UDAs is shown by sex and geostratum in the sections entitled "Analysis by Geostratum" in sections IX.C through IX.P of the Final Report.

II. STATISTICS

II.A. Statistical power

II.A.1 Was there sufficient statistical power?

II.A.2 What was the statistical power?

II.A.3 Because of the large number of participants, HTDS achieved a high level of statistical power. The final report should describe the statistical analysis and the confidence levels for the conclusions based on the least squares analysis.[based on summary]

II.A.4 I have heard from colleagues that a number of scientists consider HTDS to be inconclusive because of its low statistical power.

II.A.5 (the study was released) with the comment that the results were powerful, but other analysis suggests it is not as high.

Response: Section IX.B.4 of the Final Report contains a much more comprehensive discussion of the study's power than was provided in the draft Final Report.

II.A.6 Statistical power should be expressed as a subjective probability distribution.

Response: The HTDS investigators disagree with this approach to expressing statistical power. See section IX.B.4 of the Final Report for description of the study's statistical power.

II.A.7 How sensitive is the computed power to the targeted excess probability for disease?

Response: The relationship of the study's statistical power to the hypothesized value of the excess probability of disease or thyroid UDA outcomes is illustrated in Figures IX.B-7, IX.B-8, and IX.B-9 in section IX.B.4 of the Final Report.

II.A.8 How sensitive is the computed power to overestimation of dose by factor of three?

Response: The impact of dose uncertainties on the study's statistical power is described in section IX.B.4 of the Final Report.

II.A.9 How sensitive is the computed power to underestimation of the average background probability of disease?

Response: The impact of background rates on statistical power can be seen by comparing the results for outcomes with relatively low, intermediate, and high background rates, as described in section IX.B.4 of the Final Report.

II.A.10 On page 3 of the Introduction, you state that you had sufficient power to detect an increase of 5% in thyroid neoplasia per Gray. A clarification of this point would help us better understand what you mean by "relatively small".

Response: The subjective term "relatively small" has been deleted from the Final Report. Section IX.B.4 includes a description of the context within which to interpret the "detectable" effects.

II.A.11 (question about) the difference in interpretation of statistical power of the study between the FHCRC and CDC and why this has not been brought out publicly….

Response: Because this comment originated at a public meeting and the exact text is not available, it is not completely clear what this refers to. The implication is that the questioner was under the impression that the CDC staff disagreed with the HTDS investigators regarding the interpretation of the power of the study. There was extensive discussion between the CDC and the HTDS investigators prior to the release of the draft report regarding the interpretation of the

primary findings of the study, the power of the study, and the fact that the effects of dose uncertainty were not yet incorporated into a quantitative estimate of study power, or the quantitative estimates of risk from the dose-response analyses. Within this context the CDC staff reviewed and approved of the release of the summary findings booklet, the study fact sheets, and the prepared statement that was delivered at the press conference. There was agreement between CDC staff and HTDS investigators regarding the key messages from the study and the primary conclusions.

II.B. Uncertainty

II.B.1 The study's dose-response analysis is incomplete because the dose uncertainty has not been fully incorporated, as called for in the HTDS final analysis plan.

Response: The methods for analyses accounting for dose uncertainties are described in section VIII.C.2.c of the Final Report. Results of these analyses are included in the subsections entitled "Uncertainty" in sections IX.C through IX.Q of the Final Report.

II.B.2 What does uncertainty in dose estimates do the computed power?

Response: This is discussed in section IX.B.4 of the Final Report.

II.B.3 Maximum likelihood estimates are only one possible set of parameter values of the risk model. In fact, they may often be a next to arbitrary choice from a set of possibly applicable parameter values.

Response: Maximum likelihood estimation is a standard, widely used, and well understood technique for estimating parameters of statistical models, and is quite appropriate for the HTDS. Nevertheless, in response to the recommendation of the NRC Committee, estimates were also calculated by an alternative method, the method of least squares; see section VIII.C.2.a.4 of the Final Report. Results of both maximum likelihood and least squares analyses of dose-responses for disease outcomes and thyroid UDAs are presented in sections IX.C through IX.P of the Final Report.

II.B.4 An explanation of the sensitivity of the model to different levels of reporting of dietary intake might also help the reader in assessing the importance of misclassification due to inaccuracies in reporting of diet.

Response: The meaning of "levels of reporting of dietary intake" in this comment is unclear. The two possible sources of dietary data for study participants were the CATI, which sought detailed individual dietary histories, and the Expanded In-Person Interview, which collected no individual dietary history other than sources of cow and/or goat milk. As described in section VIII.A.1.b of the Final Report, the source of dosimetry data was investigated as a possible confounding or effect modifying factor. Results of these analyses are given in sections IX.D through IX.M, IX.O and IX.P in the tables entitled "Confounding and Effect Modification by Sex, Age at Exposure or HTDS Examination, Estimated Thyroid Dose from NTS, History of Any Cancer Other Than Thyroid and Interview Type". For none of the outcomes analyzed was there

evidence that estimation of the dose-response was significantly confounded or modified by differences in the source of dosimetry data.

II.C. Statistical (other)

II.C.1 There is concern about the characterization of our confidence in the results of the specific outcomes.

Response: Confidence intervals have been added throughout sections IX.C to IX.Q of the Final Report. These provide a description of the precision with which dose-response parameters were estimated.

II.C.2 The p-values for most analyses are very high. This signifies very little confidence in the results.

Response: This assertion in this comment that "very high p-values" signify "very little confidence in the results" is incorrect. Since the dose-response analyses of disease and thyroid UDA outcomes emphasize the one-sided alternative hypotheses that risk increases with dose, whenever the estimate of the dose-response parameter (e.g., the slope B in the linear probability model) has value less than 0, the corresponding p-value will be greater than 0.50.

II.C.3 Many of the upper bounds of 95% confidence intervals are in the positive side (implying a positive dose-response).

Response: The upper confidence limits are positive because the estimated dose response parameters (i.e., the "point estimates" of the slope B in the linear probability model) are close to zero. Confidence intervals for the dose response parameter range from a lower limit less than the point estimate to an upper limit greater than the point estimate. Therefore, for example, if the point estimate of a slope is exactly zero, the upper confidence limit will always be positive, i.e., greater than 0. Therefore the fact that the upper confidence limits are greater than 0 does not provide convincing evidence that disease risk increased with increasing dose.

II.C.4 Considering the HTDS use of surrogate dosimetries, there is an error in how the second alternative representation of exposure is described in the draft report. In section C.3 of the Discussion (IX). This was confirmed via a telephone conversation with Ken Kopecky on February 26, 1999. The final report should include an accurate description of how this analysis was performed.

Response: The definition of the high and low exposure categories has been revised from the version described in the draft Final Report. In particular, more detailed information regarding how participants' milk consumption histories were used (see section VIII.B.3.b.2 of the Final Report).

II.C.5 In doing the geostratum surrogate, was it adjusted for residence location in 1945? If not, this should be considered for inclusion in the final report.

Response: The analyses of outcomes in relation to geostratum were not adjusted for residence in 1945. Rather than perform such an adjusted analysis of differences between geostrata, a more straightforward approach would be to simply analyze outcomes in relation to residence in 1945, if the latter can be defined in a meaningful and defensible way. Such an analysis, if possible, would likely address the intent of this comment. However it is not clear how, for either kind of analysis, "residence location in 1945" should be defined for persons who lived in multiple locations in 1945. Should it be the first residence location in 1945, location of longest residence during 1945, location of residence during period of highest ^{131}I releases from Hanford, something else? All of these possible definitions are subject to the criticism that they may misclassify some participants with respect to the relative sizes of their thyroid radiation doses from Hanford's ^{131}I.

The analyses of outcomes in relation to a dichotomous exposure variable (see section VIII.B.3.b.2 of the Final Report) actually goes a long way to meeting the concern expressed in this comment. For the Final Report, this analysis has been enhanced by including both residence history and milk consumption history in the definitions of the relatively high and low exposure groups.

II.C.6 There should be discussion of mis-classification of outcomes, specifically noting results of ultrasonography QC program on page 108 of procedures section.

Response: Misclassification of outcomes is discussed in section X.C.2 of the Final Report, and the ultrasonography quality control studies are described in section V.F.9 of the Final Report. The HTDS procedures for clinical evaluation, interviews, medical record collection, and review and final diagnostic determination, described in sections V.D and V.F through V.I of the Final Report, were designed to provide highly reliable information about the presence of thyroid disease in the study participants. The primary analyses of disease outcomes were based on the most definitive diagnoses, based on a comprehensive review of all available pertinent information in the final diagnostic determination (section V.H). In addition, broader but less definitive alternative definitions were established for each disease outcome in order to investigate whether dose-response results might be influenced by the inclusion of less well-documented diagnoses (see the subsections entitled "Alternative Definitions for Diagnosis …" in sections IX.C, IX.D, and IX.F through IX.M, and IX.O of the Final Report). Any misclassification of outcomes that occurred was unlikely to be a source of bias in the estimation of dose-responses. This is because care was taken to ensure that participants did not reveal information about their possible exposure levels to the physicians and ultrasonographers at the study clinics (see sections V.F.2.d and X.C.2 of the Final Report). Also the procedures for collecting and reviewing outcome information were designed to ensure that the final diagnostic determination was made without knowledge of factors that might influence the participant's thyroid dose from Hanford's ^{131}I.

II.C.7 The sonographers had somewhat greater differences than the radiologists including discrepancies in number of nodules and presence or absence of nodules greater than 5mm. These discrepancies are not addressed and should be commented on briefly.

Response: There is little reason to compare the levels of agreement observed among radiologists to those observed among sonographers. This is because the radiologists' reviews were performed under quite different circumstances than the sonographers' examinations. As described in Section V.F.9 of the Final Report, the comparisons among radiologists were based on their reviews of videotape records of sonographers' examinations, while sonographers were compared

on the basis of the results of actual examinations that they separately performed. Therefore the radiologists saw exactly the same images, while the sonographers saw different images, as determined by their individual examining techniques.

II.C.8 The report needs more extensive discussion of multiple statistical comparisons.

II.C.9 On page 90 of section VIII and on page 13 of section IX, mention is made of conducting a large number of significance tests in the context of secondary and alternative analyses and the need for caution in interpreting a specific p-value of 0.003. This caution applies study-wide, not just to this test alone. Can the few significant results observed be explained by chance alone?

Response: The problem associated with performing multiple comparisons, i.e., the likelihood that some comparisons will be falsely significant due to chance alone, increases the risk of "false positive" results. The impact of this problem on the interpretation of dose-responses is discussed in Section X.C.3 for nonpalpable focal thyroid UDAs and for diffuse UDAs, the two disease or UDA outcomes with nominally statistically significant dose-responses (at least in the analyses that excluded participants with doses over 400 mGy).

The calculation of multiple confidence intervals is subject to a related problem. Specifically, if a confidence interval for a parameter is calculated at a given confidence level, e.g., 95%, then, loosely speaking, one can be 95% confident that the true parameter value lies within the interval. However if multiple confidence intervals are calculated, each at the given confidence level, then the overall level of confidence that all of the true parameter values lie within their respective intervals is less than the nominal level. Consider, for example, the three parameters of the sex-stratified linear probability model [1] in section VIII.C.1.a of the Final Report: one can be no more than 86% confident that all three true parameter values lie within their respective 95% confidence intervals. The approach taken to address this problem, called the Bonferroni technique, is described in section VIII.C.2.b.4 of the Final Report.

II.C.10 The words used to describe levels of statistical significance in the analysis are sometimes imprecise or contradictory. It may be inferred from the document that the authors intend to define marginal statistical significance as $0.01 <= p < 0.05$ and statistical significance as $p < 0.01$. This needs to be explicitly stated and whether or not these definitions were made a priori.

Response: Adjectives characterizing statistical significance have been omitted in the Final Report.

II.C.11 There was inconsistent applications of effect modification.

Response: The results of analyses of effect modification are given in detail for disease and thyroid UDA outcomes in sections entitled "Confounding and Effect Modification" in sections IX.C through IX.P of the Final Report. These analyses were not performed for the outcomes of thyroid cancer, other thyroid disease, or Hyperparathyroidism due to the small numbers of cases.

II.C.12 Statistical models should be specified more clearly. It was difficult to tell when models were age-, sex-adjusted and when they were not.

Response: Sex-stratified linear or logistic regression models were used for all analyses of disease and thyroid UDA outcomes in relation to estimated thyroid radiation dose from Hanford's ^{131}I or to alternative representations of exposure, as described in sections VIII-C.1 and VIII-C.2 of the Final Report. Note that this includes analyses of potential confounding and effect modification, and analyses accounting for dose uncertainties.

Analyses were generally not age-adjusted, since the cohort was defined to focus on persons with a fairly narrow range of age at first exposure to Hanford's ^{131}I, who consequently also had a relatively narrow range of age at HTDS examination (see Table IX.A-1 in section IX.A of the Final Report). Note however that age at first exposure to Hanford's ^{131}I and age at HTDS examination were included as potential confounders and effect modifiers; see section VIII.A.1.b and the subsections entitled "Confounding and Effect Modification" in sections IX.C through IX.P of the Final Report. Also, analyses of disease and thyroid UDA outcomes in relation to categorical alternative representations of exposure (geostrata or a dichotomous [high versus low] exposure variable) were adjusted for age at HTDS examination; see section VIII.A.3.b.

II.C.13 … in 1990 with preliminary results of the HEDR project, the doses looked fairly large. ..in 1994 the dosimetry was refined and the dose levels were much lower. …power calculations were borderline of whether or not the study could go forward... [he asked] why the complete analysis plan had yet to be carried out and implemented.

Response: The considerations and review leading to the decision to proceed with the Full Study are described in section V.A of the Final Report.

As described at the time the draft Final Report was released, complete results concerning the effect of dose uncertainties on estimated dose-response relationships were not available because the method of analysis proposed in the HTDS analysis plan had proven impractical. A revised approach for these analyses was undertaken for the Final Report. This revised approach is described in section VIII.C.2.c of the Final Report, and the results are presented in the subsections entitled "Uncertainty" in sections IX.C through IX.Q of the Final Report.

II.C.14 Question about whether or not by using the dose information from all the study participants, both those with CATI derived dose estimates and those with HEDR default derived dose estimates, whether or not that obscures the real dose response analysis because of the upwards bias of using the HEDR default for some of the doses and not for all.

Response: This was addressed in analyses that treated the source of dosimetry data (CATI versus Expanded In-Person Interview) as a potential confounding factor or effect modifier. The methods for these analyses are described in section VIII.C.1.b of the Final Report, and results of these analyses are described in the subsections entitled "Confounding and Effect Modification" in sections IX-C through IX-P.

II.C.15 It may be desirable to do another dose response analysis using the number (or size and number), and not just the presence of UDAs. A dose response for number of lesions might be possible for larger lesions, e.g. greater than 10 mm, but not for greater than 5 mm lesions.

II.C.16 The study should consider if a dose response analysis of the number and size of UDAs is feasible and should be performed (taking into account my caveat regarding sonographer concordance).

Response: The suggested analyses can be found in section IX.P.2.k of the Final Report (see also sections VIII.C.1.d and VIII.C.2.a.3).

II.C.17 .. it is important to realize the difference between a dose study and the link issue. paraphrased: if the study doesn't find a dose response it doesn't mean there isn't a link.... that is not the way the study is set up ... .

Response: The HTDS was basically a typical epidemiological study, similar in design and execution to a very large number of other studies that have been conducted over the years to investigate the potential health impacts of exposures to a wide variety of potentially harmful agents, including ionizing radiation. The methods that have been developed for these studies take into account the fact that individual cases of disease, or of other outcomes such as thyroid UDAs, cannot be directly linked or attributed to a particular exposure. This is because (1) the outcomes being studied, thyroid and parathyroid disease and thyroid UDAs in the case of the HTDS, can all occur spontaneously, i.e., in the absence of exposure to ^{131}I, and (2) there are currently no known markers or other characteristics that distinguish cases of disease caused by radiation exposure from the spontaneous ("background") cases. Since it is not possible to detect direct, causal links between exposure and outcomes, an epidemiological study is designed to search for statistical evidence of associations between exposure and disease risk. The statistical results of such a study, while they cannot provide absolute proof of the presence or absence of causal links between exposure and outcome, nevertheless provide information of great importance to the public, the medical community, health officials, and scientists. The inappropriateness of requiring absolute proof of the presence or absence of a causal link, and ignoring statistical evidence for the presence or absence of exposure-outcome association, is perhaps best illustrated by the example of smoking. The tobacco industry argued for decades that the harmful effects of smoking were not "proven" because the evidence for those effects, as overwhelmingly compelling as it is, came largely from epidemiological studies that showed statistical associations between smoking and disease.

II.C.18. The report should emphasize prominently the difference between the primary analyses, formulated as part of the study design, and secondary analyses, conducted after the data have been obtained. [Suggest this is moved into Statistics somewhere]

Response: In sections IX.C through IX.M, IX.O, and IX.P, the primary analyses (i.e., those based on the primary definition of the disease outcome and the sex-stratified linear model) are placed in subsections entitled "Primary Analysis." These are subsections 2.a in IX.C through IX.M and IX.O, and 2.a, 3.a, 4.a, and 5.a in IX.P. As noted in section IX.N.1, the primary analysis was not performed for the outcome of Other Thyroid Disease since there were too few cases for meaningful analysis.

II.C.19 Why not use confidence interval instead of standard error

Response: Confidence intervals, calculated using the Bonferroni method to adjust for the simultaneous estimation of multiple parameters, have been added to dose-response results throughout chapter IX of the Final Report (see also section VIII.C.2.b.4).

III. DOSE RESPONSE

III.1 Chronic low dose radiation is more effective in producing health effects

Response: The assertion in this comment is not supported by the medical and epidemiological literature. It has been well substantiated that acute, high dose radiation exposure is more harmful and associated with numerous short term and long term health effects, than is chronic, low dose radiation. See section II.B of the Final Report for a review of the current literature regarding radiation and thyroid disease risk.

III.2 A least squares analysis would show the actual relationships between the dose and the effects. It is obvious from analysis of Figures 1 and 2 that a least squares analysis would show that the frequency of cancer decreases with dose.

Response: The method of least squares is an alternative to the method of maximum likelihood for estimating the parameters of the linear dose response models. These two methods can be expected to give similar though not identical results for disease and thyroid UDA outcomes. Although it adds little to the analysis and has no impact on the study's findings, least squares estimation of linear dose response models for disease and thyroid UDA outcomes has been added. The application of least squares is described in section VIII.C.2.a.4 of the Final Report, and the results of least squares estimation are described in the subsections entitled "Primary Analysis" in sections IX.C through IX.P of the Final Report.

IV. CONTROL POPULATION

IV.1 Why wasn't there a control population?

IV.2 I think a wider study is called for and a control area is needed that is outside the reach of the farmers market.

IV.3 The decision to use a low-dose rather than no-dose comparison group may also limit the study's ability to detect effects due to exposure to iodine 131.

Response: As explained in section IV.A of the Final Report, the HTDS adopted the approach of using one population comprised of individuals with different levels of exposure to radiation rather than two separate populations (one exposed and one unexposed) to see if there was a relationship between exposure to Hanford radiation and the risk of thyroid disease. This approach has been used extensively in assessing the effects of radiation exposure in human populations. It is a common design in epidemiology, and has been employed in studies of atomic bomb survivors in Japan, in numerous studies of people exposed to radiation through medical procedures, and in the

study of people exposed to radiation from atmospheric testing in Utah. This method is superior to the alternative approach of attempting to compare thyroid disease occurrence in a cohort under extensive study such as the HTDS cohort with that in a separate population presumed to be unexposed to radiation. This is because thyroid disease rates may be a function of a number of factors other than exposure to radiation. These factors may differ considerably between different populations, particularly if one population is under careful study and diagnostic evaluation. Such differences can include: 1) the methods of diagnosis employed; 2) the extent to which diagnostic tests are implemented in a population (i.e., the thoroughness of the diagnostic process); 3) the dietary practices of the population; 4) the level of stable iodine in the diet; and 5) the composition of the population according to age, gender, and ethnicity. To the extent differences in such factors exist, it would be impossible to attribute any differences in thyroid disease rates observed to Hanford radiation exposure, as opposed to one or more of these other factors. The approach used in the HTDS is also superior to one that would implement the full HTDS protocol in a population geographically removed from the Hanford, in an attempt to include persons with no exposure from Hanford radiation. Although the methods and thoroughness of the diagnostic evaluation would be comparable under such circumstances, it would still not be possible to ensure comparability between the two study populations regarding the other types of possible differences listed above that could influence thyroid disease occurrence. Thus, to ensure as much comparability as possible regarding factors other than radiation that can influence the occurrence of thyroid disease, all comparisons of thyroid disease rates in relation to thyroid radiation dose level were made within the defined cohort.

V. STUDY DESIGN AND SELECTION CRITERIA

V.1 *To exclude (name) [born outside of study area] from any consideration that her health might have been injured due to Hanford emissions is an affront to most intelligent people. We believe that this study did not involve a large enough sampling nor did it cover enough years. Why did it stop at 1946? Was it assumed that nobody born beyond 1946 could have been affected?*

V.2 *I would like to know why the study was done on people born in 1940-46 when people were exposed during 1944-1957?*

V.3 *Says study was not "fair" since not everyone with thyroid disease was included.*

V.4 *Did the study include the "right" counties? Didn't we miss legitimate counties?*

V.5 *Why is Okanagon County a low dose area?*

V.6 *Why wasn't the higher population from Spokane added?*

V.7 *Why weren't the migrant worker population and Native Americans in the study?*

V.8 *Even though I was born in Benton County in 1941, we moved to San Diego a couple years later. Except for an occasional visit to grandparents, I did not spend much time in that geographical area. And, Benton County is not normally 'downwind' from Hanford anyway. Which brings the sampling into question in my opinion.*

V.9 *My ex-wife [who had Hashimoto's] was born in southern Idaho, but her family moved to Cheney, Washington, when she was very young and she had lived there until adulthood. The study people refused to accept this information since she was not born in the counties they were sampling. This told me that they just didn't want to hear the truth, and that a vast number of "Downwinders" would not have a chance to be a part of the study.*

V.10 *How a bunch of so-called "experts in their field" can make the sweeping statement that there is no cause-and-effect between the Hanford emissions and thyroid disease is beyond my understanding. Nobody studied [my wife] or the year she was born in. How can [my wife's] case be so cavalierly dismissed when she was never studied or examined as an individual?*

V.11 *Were they even aware that a portion of Grant County is within the boundaries of the Hanford Nuclear Reservation?*

V.12 *I am dubious of the study's age group and geographical mix.*

V.13 *Spokane's directly NE-Downwind- from Hanford. Why wasn't sampling done from a larger, concentrated population?*

V.14 *It is incomprehensible that the Hanford thyroid study did not include 25,000 students at Washington State University for that period of time.*

Response: It is not possible to include in a study like the HTDS everyone who was ever potentially exposed to Hanford radiation. More importantly, it is not necessary to do so in order to achieve the primary objective of determining whether Hanford radiation exposure resulted in an increased occurrence of thyroid disease. If the study is conducted correctly, the results will be meaningful to a much broader population of people than just those relatively few who actually were in the study. The most important principle to follow in conducting a study like this one is to select people for study in an unbiased manner; that is, *not* based on the knowledge that they lived around Hanford and developed thyroid disease, or that they didn't live around Hanford and didn't develop thyroid disease. Such a design is "fair" because it includes people who were potentially exposed to Hanford's ^{131}I, without regard to whether or not they developed thyroid disease. It was critical that we identified a group of people exposed to Hanford radiation, and then determined in an unbiased way exactly what happened to them thereafter regarding the development of thyroid disease. The most important considerations were to include people who were exposed to Hanford radiation, to include persons with the highest exposures as well as those with little or no exposure, to select people without knowledge of whether they have thyroid disease, and to collect information from every study participant in exactly the same way regarding their exposure and their thyroid disease status.

Because we did not know at the start of the study which individuals were exposed to Hanford radiation or how much exposure they might have received, for the purposes of subject selection only, residence at time of birth acted as a surrogate for the anticipated radiation dose to the thyroid from Hanford. Individual thyroid radiation dose could only be estimated from data collected during the study. As noted in section IV.A of the Final Report, preliminary findings from the HEDR project at the time the study began regarding meteorological conditions affecting the deposition and concentration of radioactive iodine in vegetation, and the patterns of milk production and consumption by county, indicated that persons with the highest thyroid doses were most likely to have lived in the area encompassed by Benton, Franklin, and Walla Walla

counties. Thus, these counties were targeted as areas where we might identify persons with the highest doses from Hanford radiation. The selection of cohort members was also extended to include three counties on the Canadian border north of the Hanford site (Okanogan, Ferry and Stevens). These counties were selected because, based upon the information available at the time regarding possible radiation doses to the thyroid, they could be expected to contribute some individuals with very low radiation doses to the thyroid from Hanford. In addition, persons living in these counties would likely be comparable to the group of those who did receive a thyroid dose in terms of other factors which could potentially influence the risk of thyroid disease (e.g., geography, urban/rural composition, occupational factors, socioeconomic factors, age, ethnicity, sex). It was also important that similar opportunities and resources existed to identify and trace persons in these counties as there were in the group that lived in counties closer to Hanford.

Preliminary estimates from the HEDR project also suggested that the highest thyroid doses were most likely to be in persons exposed as infants or children during the first years of Hanford operations. This is because infants and children receive higher thyroid doses per unit exposure due primarily to the small size of their thyroid glands, and existing literature suggests that radiation-induced thyroid disease (and possibly hyperparathyroidism) is greatest among those exposed at youngest ages. For this reason, the study focused on persons who would have been young children at the time that the majority of releases of radioactive iodine from the Hanford facility occurred (1944-46). The best way to identify people who would have been young children during this time in an unbiased manner was to use a roster of all births that occurred around that time period in the counties of interest. We selected persons born from 1940-46 to achieve this end, which meant that the cohort would contain persons with exposure beginning as early as the prenatal period, and as late as age three. We did not purposefully exclude any particular group (e.g., Native Americans). This is not to imply that persons born after that time were not exposed, or potentially affected. This approach was taken to focus on those who most likely received the highest exposure, and who were likely to be most sensitive to the effects of that exposure. An additional benefit of choosing this young age group was that mothers and close relatives of persons born from 1940-46 would more likely be alive and available for interview compared to those of persons born earlier.

V.16 How do we know that Hanford emissions, as well as emissions from other nuclear projects and testing, did not contaminate the entire food chain nationwide, thereby causing thyroid disease on a large scale? If this were the case, then of course a select few Hanford downwinders thyroid problems would not stick out, or be obvious.

Response: The results of the Hanford Environmental Dose Reconstruction (HEDR) Project strongly suggest that the doses caused by ^{131}I released into the atmosphere from Hanford were highest in people who lived in the counties immediately to the east and northeast of Hanford (see, e.g., Figure IV.A-1 in section IV.A of the Final Report) during the first several years of operations at Hanford, i.e., the years of highest ^{131}I releases. This does not mean that people who lived in other areas were not exposed to Hanford's ^{131}I. Indeed results of the HEDR Project indicate that people who lived outside the region shown in Figure IV.A-1 during 1945-57 were probably exposed to Hanford's ^{131}I. However the further away from Hanford a person lived, the lower his or her thyroid radiation dose from Hanford's ^{131}I is likely to be. This is important because studies of the health effects of radiation exposure consistently show that those effects are dose-dependent. That is, the risk of having a health effect increases with increasing dose. Therefore, as described in section IV.A of the Final Report, the study was designed to include as many of the most highly exposed people as possible, since they would be most likely to have

suffered health effects from Hanford's ^{131}I. In addition, the thyroid doses from Hanford's ^{131}I were expected to be larger than those from atmospheric fallout from the Nevada Test Site or other nuclear weapons tests around the globe for many study participants. Therefore an appropriate analysis of the dose-responses for thyroid health outcomes in relation to estimated dose from Hanford's ^{131}I could be expected to detect any increases in thyroid disease related specifically to Hanford's ^{131}I.

V.17 Did you include all persons that could be found and who volunteered to be included? The statements on page 10 are too vague. Why were 909 potential participants not included? Explain what effect not including those 909 persons might have had on the results.

Response: Every eligible potential participant who was selected for the study, was located, agreed to participate, and attended an HTDS clinic was included in the analysis, except for seven who were nonevaluable according to the study's predefined criteria (see sections IV.B and IX.A of the Final Report). Detailed information is provided in sections V.B and V.C of the Final Report to describe how many of the 5199 individuals originally selected for the study actually participated and the reasons for nonparticipation. A more detailed discussion of the possible effects of nonparticipation is provided in section X.C.1 of the Final Report.

V.18 Lincoln County, with the highest Multiple Sclerosis incidence on the planet, should've been look at too.

Response: As noted above, the counties from which participants were selected were chosen based on the likelihood that residents would have been exposed to atmospheric releases of ^{131}I from Hanford. From the information available at the time it did not appear that Lincoln County residents would have likely received as much exposure as residents of the counties that were selected. As discussed above, it is not necessary to include residents of other counties, such as Lincoln, in the actual study in order for the HTDS results to be meaningful to those residents. Also, as described in section II.A of the Final Report, the HTDS was specifically mandated to investigate thyroid disease, not other disorders.

V.19 The report of the HTDS does not include a section on dietary intake methodology, including the strengths and weaknesses of different approaches to obtaining dietary intake information, such as use of proxy respondents and accuracy of reporting intake from many years ago.

V.20 The study methods did not seem to include any attempt to ask questions that would allow for assessment of internal reliability of dietary recall.

V.21 It is difficult to get an overview of who provided dietary information for what proportion of the final HTDS study population. We urge you to summarize this information in Section V or Section VIII.

V.22 While you assessed thyroid disease using exposure based on both the reported dietary intake and the HEDR reference diet, you did not seem to include any comparisons of the reported diet to the reference diet.

Response: Obtaining information about specific aspects of each participant's dietary intake when he or she was an infant and small child, more than forty years after the fact, was a major challenge faced by the study. An extensive discussion of alternative methods was not included in the report because there were few feasible options. A discussion is presented of the need to interview proxy respondents, because the participant him/herself would have been too young at the most relevant times to remember (see section V.D.1.a of the Final Report). A rather extensive discussion is also presented to describe the special attempts made to modify the more standard approach of interviewing typically used in epidemiologic studies to include elements based on principles of cognitive interviewing to enhance memory and recall (see section V.D.2.a of the Final Report). Assessment of the internal reliability of the dietary questions, using such standard techniques as re-interviewing, was not deemed appropriate under the unique circumstances of this study and the data collection methods used, and would not have provided very informative results.

The proportions of living evaluable study participants whose doses were estimated from dietary and other data provided by their CATI respondents are summarized by in-area status in Table IX.B-1 of the Final Report. The relationships of CATI respondents to their corresponding participants are summarized in Table V.D-5 of the Final Report.

Comparisons between dietary data reported by CATI respondents and HEDR defaults were not performed because the two were derived from widely different sources. As described in section V.D of the Final Report, reported dietary intakes were obtained from CATI interviews of respondents with direct personal knowledge of their corresponding participant's life during 1944-57. The CATI respondents were mostly elderly, most commonly the participant's mother, and were asked to recall information from a period 35-50 years before the interview. In particular they were asked to provide point estimates of the quantities of food and milk products consumed during that period by the study participant, and by the participant's mother if she was pregnant with or breastfeeding the participant. In contrast, the HEDR default dietary data was derived from data collected during the Nationwide Food Consumption Survey of 1977-78, which were adjusted to reflect food consumption in the period of interest (1945-57), and consisted of empirical distributions of quantities consumed, rather than point estimates. (6).

V.23 *I would consider reviewing all cases of malignancy and a subset of the remaining cases by two or more experienced thyroid cytopathologists. Also, I would ask them to review the cases with hypocellular samples with abundant colloid to determine whether they agree with their classification.*

Response: A comprehensive review of all 259 biopsy specimens (rather than a subset) was done and the results summarized in the Response to NAS document (see Appendix 24). Cases of malignancy could not be reviewed since the HTDS no longer had access to those specimens, however all HTDS diagnoses of cancer were based on separate reviews by the HTDS pathologist of the original pathologist's interpretation. Of 19 cases, there was complete agreement with the diagnosis of thyroid cancer in 17 cases. For one case, the slides were not available but the HTDS pathologist reviewed the initial pathology report, performed by a nationally recognized AFIP pathologist, and expressed confidence in the reported diagnosis. For the final case, there was disagreement between the original pathologist, who did not find thyroid cancer, and the HTDS pathologist, who found a 4 mm focus of papillary carcinoma.

With regard to hypocellular specimens with abundant colloid, all of these cases were reviewed. There was no disagreement by the reviewing cytopathologists in any of these cases to suggest that a neoplasm or carcinoma had been missed.

These results, in addition to the comprehensive review of all FNA specimens (see Appendix 24, Response to NAS), strengthens the validity of the approach in the original study design of having a single, experienced cytopathologist review all of the FNA specimens.

V.24 Page 116. In this section it is stated that "...four participants were determined to be non-evaluable". On p.188 the number of non-evaluables is given as six. I don't know which number is correct, but I believe that the same number should be given in both of these places.

Response: Section IX.A of the Final Report contains information on the number of participants who were eligible but nonevaluable. The correct number is seven. Six did not have complete residence histories for the period from the beginning of their possible exposure to $^{131}I^{-}$ from Hanford through the end of 1957, and the seventh had a tracheotomy tube in place which prevented palpation of her thyroid at her HTDS clinical examination.

V.25 There is no sense of how many nodules greater than 1.5 cm were biopsied or unbiopsied (i.e. ultrasound detected, nonpalpable nodules that remained unbiopsied).

Response: Among participants who had nonpalpable ultrasound-detected abnormalities, 34 had dimensions greater than 1.5 cm in three dimensions. Of these 34 participants, 25 underwent FNA biopsy while the remaining 9 did not undergo biopsy. Those not undergoing biopsy either declined FNA or in a few cases it was not recommended since the recommendation to biopsy such nodules was not instituted until after the first year of the study. For the 25 participants who underwent biopsy, 23 had adequate biopsy specimens. All of these were benign except one, which was suspicious for a follicular neoplasm. There were no cases of thyroid cancer.

V.26 Data can also be presented starting with the nodules that were biopsied and determine how they were discovered (palpation, ultrasound) and show the pathological results and final assessment.

V.27 I believe that it would be very helpful to have tables that summarize "paths to diagnosis". I believe that there should be about three of these tables, one for cancer, one for benign, and for all nodules.

Response: An analysis of the “pathway to diagnosis” has been performed for all of the diagnoses made by FNA biopsy in the HTDS (see sections IX.C.1.a and IX.D.1.b). Tables have been provided for thyroid cancer (Table IX.C-3) and for benign nodules and nodules suspicious for follicular neoplasm (Table IX.D-9) These analyses, done on 256 participants who had FNA procedures performed, are discussed in these sections of the Final Report as well as in the Discussion (X.C.2).

V.28 The FNA results are somewhat unclear in the draft report. For instance, on page 8 of the executive summary it states that 259 participants had FNA. 62 (24%) were recommended to have further biopsy but in the post-clinic medical records review it states medical records documenting further diagnostic studies were requested for 35 participants (page 9 of executive summary). What happened to the other 27 participants (62 less 35)? Are these the patients who have a nodule which is suspicious for malignancy or neoplasm (Background, page 15)? But this number appears to be 16 (the difference between line 2 on Tables VIII-18 and VIII-22 and -23).

V.29 Sixty-two of 259 FNA (24%) were recommended to have further biopsy or surgery. Twelve of the participants had thyroid cancer and 14 follicular adenoma. This leaves 13% of the FNAs needing further evaluation. The report should go through these cases and show what percent of cases actually needed confirmation due to the uncertainty of the FNA/pathologist. They should compare the nondiagnostic percentage in this study to published thyroid FNA results.

Response: These comments concern two related issues: the completeness of follow-up for persons having FNA and the percentage of nondiagnostic FNA procedures. Regarding the first issue, of the 259 participants who underwent FNA, 47 (not 62) were recommended to have further biopsy or surgery. (The 62 referred to in the Draft Report also included individuals who were to be followed for nuclear medicine scans, additional lab work, etc, but not exclusively because of FNA results; see section V.H.3.a of the Final Report). Of the 47 who were recommended to have further biopsy or surgery, 30 did so and were consequently diagnosed with thyroid cancer (12 cases), follicular adenoma (5 cases), or benign nodule other than follicular adenoma (13 cases). The remaining 17 participants were classified as Suspicious for Follicular Neoplasm because they did not go on to have further biopsy or surgery. See sections VIII.B.3.c and IX.D.1.a.1 of the Final Report for further discussion of this category.

The second part of this question refers to nondiagnostic FNA rates. In interpreting these data, it is important to note that the amount of specimen material obtained by the HTDS physician team exceeded what is typically obtained in clinical practice. For example, the number of aspirations per nodule typically was between 4-10 with 10-20 slides of material provided to the cytopathologist for review. The number of nondiagnostic aspirates (hypocellullar or acellular specimens) was 7 (2.7% of the 259). In addition there were 18 persons with a single nodule for which the FNA showed abundant colloid but hypocellularity. These were classified as benign. This classification was made in part due to the confidence of having extensive sampling as noted above in this study. However, it is acknowledged that a suspicious or malignant lesion cannot be entirely ruled out in such cases. Thus, if we assume these 18 cases to also be nondiagnostic and add them to the 7 true nondiagnostic cases noted above, this yields 25 cases (9.7%) as the upper bound of inadequate or nondiagnostic specimens in this study. Thus, the rate of nondiagnostic FNA specimens in this study is 2.7-9.7%, a figure that is well within the 2-20% figure in the published literature.

V.30. The Discussion talks about thyroid neoplasia (Discussion, page 15) and the Utah study, but are the results comparable? Is it reasonable to perform a dose response analysis on different combinations of neoplasms? That is 1) adenomas and carcinomas together, excluding colloid and non-neoplastic nodules and 2) adenomas and carcinomas and nodules suspicious for malignancy, excluding colloid and non-neoplastic nodules?

Response: We understand this to be a question about whether the HTDS performed an analysis identical to the one performed in the Utah Study which showed a statistically significant dose-response for thyroid neoplasia (thyroid cancer plus benign follicular neoplasms). The HTDS undertook an even more comprehensive approach to define alternative definitions of thyroid outcomes in order to determine if a true dose-response relationship might have been missed in the primary analyses. These alternative outcome definitions included the following: benign nodules plus nodules suspicious for follicular neoplasm, benign nodules excluding non-neoplastic disease (such as Hashimoto's or Graves), benign nodules detected only by palpation (prior to ultrasound review), benign colloid nodules (see section IX.D.1.a of the Final Report). In addition the HTDS investigated thyroid neoplasia, which was defined as all thyroid cancer and all benign follicular neoplasms (excluding colloid nodules). This was identical to the outcome of thyroid neoplasia defined in the Utah study. Dose-response analyses were performed on all of the above alternative outcome classifications (see section IX.E of the Final Report).

V.31 To confirm the findings of a lack of a dose response relationship, and to investigate further the role of palpation and ultrasound, I suggest carrying out separate analyses for the endpoints of palpable nodules and ultrasound nodules larger than 1.5 cm in average dimension.

Response: We interpret this comment as requesting one dose-response analysis for palpable nodules and a second dose-response analysis for ultrasound nodules (palpable and nonpalpable) which are greater than 1.5 cm in average dimension . The dose-response analysis for "Any solitary palpable nodule" can be found in Section IX.F.1.a.1 and IX.F.2.c.1). Regarding the ultrasound nodules, a comprehensive analysis has been performed for focal ultrasound-detected abnormalities by size: one for those greater than 5mm, one for those greater than 10 mm, and one for those greater or equal to 1.5 cm in average dimension. These analyses can be found in Section IX.P.1.a.1 and IX.P.2.b. In addition, a separate analysis (see Section IX.D.1.a.3. and IX.D.2.c.3) has been done for benign nodules detected by palpation (excluding those found with the assistance of ultrasound).

V.32 I found that one table in the analysis plan that was not in the final report. This was the number of palpable nodules that were not confirmed by ultrasound. Since the analysis plan was reviewed and agreed to by several groups, it is best to complete all aspects.

Response: This table has been added to the Final Report (section IX.D.1.a.3)

V.33 I believe that the description of multinodular goiters and multinodular glands and their overlap with the category of thyroid nodules should be made clearer.

Response: As described in section IV.C of the Final Report, the only difference between multinodular gland and multinodular goiter in that the estimated size of the gland in the latter category is greater than 2-fold enlarged. Dominant palpable nodules in a multinodular gland or goiter were biopsied in the same manner as solitary thyroid nodules.

V.34 The laboratory findings should be scanned to be certain that the appropriate units are stated whenever a value is given. Also, while the various TSH methods are described, it would be helpful to describe them by their level of sensitivity.

Response: The appropriate units have been included in the Final Report. Detailed characteristics (such as sensitivity) of the various laboratory tests used are not provided as they do not alter or influence the criteria for diagnosis for a given outcome.

V.35 Has the incidence of juvenile onset thyroid disease been looked at?

Response: Any participant with a history of thyroid disease, whether as a juvenile or adult, was asked to release medical records. The information obtained was then incorporated into the HTDS results regardless of the age at which the diagnosis was made. Thus, even though the actual age at onset may not be available, the diagnosis of any thyroid disease in a participant is included in the HTDS results.

VI. COMPARISONS

VI.A. Comparisons to literature or other studies related to dose-response, radiation and thyroid disease.

VI.A.1 How do these findings compare with the literature (regarding radiation and thyroid disease)?

VI.A.2. What does the literature say about dose-response?

VI.A.3 Do these results agree with "current knowledge" (about radiation and thyroid disease?)

VI.A.4 How does [the study] fit into the whole spectrum of other exposures of I-131 and thyroid disease?

Response: The answers to these four questions come from hundreds of scientific studies done over the last 75 years on the effects of radiation and thyroid disease. It is well known that some types of radiation exposure can cause thyroid disease. However, the frequency and type of thyroid disease, and age at onset of the disease, all depend on many factors such as the type of radiation exposure, the route and duration of exposure, the age of exposure, and the magnitude of the dose. These and other factors determine the risk, or chance, of actually getting thyroid disease. For some circumstances of radiation exposure, the chance of getting thyroid disease during a person's lifetime may be high while in other circumstances of radiation exposure the risk may be so low that an individual may never experience thyroid disease from that exposure.

Since there is an extensive scientific literature on this subject, the response to these questions will necessarily be abbreviated. In general, the most common types of thyroid disease that have resulted from radiation exposure are benign and malignant thyroid masses. While hypothyroidism can result from environmental exposures, the doses must be exceedingly high to cause this problem. There are relatively few reports that suggest that hyperthyroidism results from radiation exposure. Some studies have suggested that autoimmune thyroiditis, which is quite common in

the general population, may be increased after radiation exposure. However, clear evidence for this is lacking and much further study is needed before this can be stated with certainty.

The literature shows fairly clearly that radiation exposure from external gamma radiation produces a linear dose response. Again this is subject to the many different risk factors that determine whether radiation exposure in a given circumstance actually causes a thyroid disease. For example, it was clearly shown that young people (less than 15 years at the time of exposure) who were exposed to A-bomb radiation at Hiroshima or Nagasaki developed excess thyroid cancer with a linear dose-response. However, those persons who were older than 20 years had almost no risk of thyroid cancer during their lifetime even though they were exposed to the same levels of radiation. The type of dose-response for exposures involving radioactive iodine (e.g., Chernobyl) is much less clear. Additional information on this issue has been added to this Final Report (see Section X.D).

The response to the question of whether the HTDS results agree with "current knowledge" is complex. The HTDS results are "consistent" with the world literature regarding radiation exposure and thyroid disease in the sense that many of the factors that would predict low risk of thyroid disease are characterized by the HTDS cohort of participants. Although the cohort was composed exclusively of people who were in utero, infants, or young children at the time of greatest exposure, and therefore the most likely persons to develop radiogenic thyroid disease, other factors of the exposure might be predictive of low risk. The most important of these factors is probably the low magnitude of the radiation dose. A second factor is that these low doses were accumulated over months or years whereas in other populations exposed to environmental radiation, where the risk of thyroid disease was significant, much or all of the exposure happened acutely, usually over hours. Another factor may be that the exposure from Hanford was almost exclusively ^{131}I and did not include significant external radiation or other types of radioiodine which were present in other population exposures.

VI.A.5 An explanation of the reasons for differences in the findings of NTS and the HTDS would be helpful in assessing the HTDS results.

Response: With regard to the question of NTS exposures we interpret this question to mean the Utah Study, which evaluated the risk of thyroid disease from exposures from the Nevada Test Site. We have provided additional discussion in the Final Report (see section X.D) regarding the differences in both the type of exposures in these two studies, as well as the differences in results.

VI.A.6 Questions about the correlation to Dr. Rudy Nussbaum's 801 health surveys for downwinders.

Response: Results of scientific investigations depend greatly on study design. Different study designs may produce different results, even though each study is trying to answer the same scientific question. The "801 Health Survey" was based on completed questionnaires received from approximately 800 individuals who responded to a general request for people who considered themselves to be Hanford Downwinders to fill out a questionnaire. Surveys of this type can be very misleading (i.e., biased) if those who choose to reply are systematically different with respect to their disease status and their exposure experience. For example, if those who have thyroid disease and who were exposed to Hanford radiation are more likely to participate than those who don't have thyroid disease (but were also exposed to Hanford radiation), the results will incorrectly indicate that there is an association (a relationship) between exposure and thyroid disease. The HTDS was designed to limit this kind of bias by following an entire cohort of people

over a long period of time to determine the likelihood that those exposed to Hanford radiation were at an increased result of developing thyroid disease as a result of their exposure. A survey like the "801 Health Survey" is not able to answer this question.

VI.A.7 This study seems to assert that its results are superior to other work that has been done on I-131.

We do not know the origin of the comment this question is referencing. With regard to studies of Hanford ^{131}I exposures, the HTDS is the only study of its kind that has ever been conducted. With regard to any study of ^{131}I, the HTDS is unique in terms of the degree of peer review and quality control that has characterized the study, and has been conducted in as rigorous a manner as any other published study.

VI.A.8 What is the incidence of thyroid cancer in all persons born in the US between 1940 and 1946?

There are no data on the incidence of thyroid cancer in the United States as a whole. The only source of population-based cancer incidence data is the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. This program consists of approximately ten cancer registries in locations throughout the United States. Although the areas covered include urban and rural areas in all different regions of the U.S., they are not necessarily representative of the overall U.S. population. The program did not begin operation until 1973 in some areas and 1974 in other areas. Thus, it is not possible to determine the exact answer to this question. In general terms, the incidence of thyroid cancer in adults in the U.S. (persons born between 1940-1946 would be adults now), based on recent SEER data, is approximately 4 per 100,000 per year. The incidence is higher in females than males (approximately 6/100,000 per year vs. 2/100,000 per year, respectively) and increases with age. Thyroid cancer under age 20 is very uncommon in the U.S.

VI.A.9 Did any of the 19 persons in the study identified as having thyroid cancer know they had thyroid cancer in advance of the study?

Response: Of the 19 persons identified with thyroid cancer in the HTDS, 7 had the diagnosis and treatment prior to entering the HTDS, 12 persons had the diagnosis made by HTDS physicians. In addition, one individual reported a prior history of thyroid cancer for which medical records were unavailable. Therefore, 8 of 20 persons with a diagnosis of thyroid cancer knew of the diagnosis prior to their participation in the HTDS (see section IX.C.1 of the Final Report).

VI.A.10 Question about whether 2,000 people with thyroid disease is exceptional, normal or below normal.

VI.A.11 Is there a higher percentage of thyroid malfunction in Hanford than nationally?

VI.A.12 The population also had a surprising amount of thyroid disease, although its prevalence was not dose related. These findings raise questions that should be answered with regard to the population studied, although it is hard to see how significant bias could be introduced considering the way in which the population was selected.

Response: With regard to the above three questions referring to comparison of thyroid disease in the HTDS cohort with that nationally, an entire section has been added to the Final Report which provides a review of the world literature on the prevalence of thyroid diseases (see section X.E). This section compares the results from that literature to the results obtained from the HTDS.

VI.A.13 It is surprising that the presumably normal study population had such a large number of prior diagnostic X-ray exposures. That 36% of the population had prior upper GI series and 34% had X-rays of the head, to say nothing of the 24% of the population that had a CT scan of the upper body raises a question as to whether the selected study population is truly representative. The availability of an appropriate control population for comparison would add another layer of reassurance. And informal and anecdotal query of a limited number of diagnostic radiologist colleagues suggests that these numbers are beyond what might be expected in ordinary practice with a "normal" population.

Response: The HTDS did not evaluate the actual number of x-ray procedures but rather whether or not a participant or his/her CATI respondent reported that the participant had any history of such exposures. Independent validation of these self-reports was beyond the scope of the HTDS. Furthermore, there are no studies of the frequency of use of x-rays and other procedures in unselected populations from that time period which might provide a suitable comparison. However, the question of whether the HTDS population is "representative" regarding the use of such procedures is not of direct relevance in evaluating the dose response with Hanford radiation. The more important question is whether the reported frequency of the procedures among study participants confounded or modified the effect of Hanford radiation. This was evaluated formally in the analyses of each outcome, and there was no evidence of confounding or effect modification according to the number of self reported medical radiation exposures (see the sections entitled "Confounding and Effect Modification" in sections IX.D through IX.M, IX.O, and IX.P of the Final Report).

VII. MORTALITY STUDY AND ANALYSIS

VII.1 I trust your study is also covering those people who lived in the area but who have died.

VII.2 These [deceased] lost souls most definitely need to be included in all these studies.

Response: As described in section V.B and Appendix 23 of the Final Report, the HTDS attempted to identify all potential participants who were deceased among the original 5199 identified for study, regardless of where they resided when they died. The study also requested a

copy of the death certificate for all those confirmed as deceased. Of the 543 individuals confirmed as deceased, a death certificate was obtained for 504 (93%).

VII.3 *I noticed that 541 people were deceased. Please tell me how that compares with traditional mortality tables, and should I be concerned? As I looked at the tables, it seems that the risk of thyroid problems was actually reduced for those who were exposed.*

VII.3 *It is of interest and a little disturbing that mortality in the cohort was 20% higher than expected. The primary contributor to this number was apparently congenital abnormalities and perinatal problems, which amounted to an excess of over 2 times that, expected. This could hardly be a radiation effect since many of these births occurred before Hanford went into operation, but further discussion would be helpful.*

VII.4 *They have one hit - higher mortality. How does the study deal with this? They shush things. They say there were more dead people before and afterwards so they won't really worry about it.*

VII.5 *Page 6 of the Summary Final Report: Researchers didn't do any studies to make assertion that "although there is a high death rate and although the reasons for this higher death rate are not known, it is not likely that it is related to radiation from Hanford."*

VII.6 *The impression being given is that radiation is not a concern for Downwinders. I am concerned that they do not know why people died, they might have had thyroid cancer.*

Response: Based on the information obtained regarding cause of death from the death certificates for deceased potential participants, an analysis was conducted to investigate whether the mortality experience in the HTDS cohort overall was unusually high, relative to what would be expected based on the mortality experience of the population of the same region over the same time period. Additional analyses were conducted to determine whether there was any indication of an excess in mortality in the HTDS cohort from conditions that might be related to one or more of the primary outcomes of interest regarding thyroid disease. In summary, there was no overall increase in total mortality over what would be expected based on the mortality experience of the population of Washington State during the same time period. This was true for both men and women. However, there was an excess in deaths due to conditions of the perinatal period, which was found in both men and women.

Findings based on preliminary analyses which were included in the Draft Final Report (January 1999) indicated a similar excess in mortality due to conditions of the perinatal period, and also suggested a 20% excess in mortality overall. However, those findings were based on a more crude analysis which included in the cohort only those who attended a HTDS clinic, as well as those who died. The present analysis is more complete, and includes all those located from the original cohort of 5199 individuals, regardless of whether they participated in the study or not (and including those who died).

A detailed description of the methods used to assess mortality in the HTDS cohort and the full results of these analyses are presented in Appendix 23 of the Final Report. In addition, the Discussion section (Section X.C.1) has been expanded considerably to consider the possible impact on the radiation dose-response of deaths in the cohort.

VII.7 Year of birth as an indicator of exposure can be somewhat misleading when is dealing with congenital anomalies or pregnancy complications. Exposure at conception or in early pregnancy may be relevant, and this might be in the previous calendar. If you have the actual birth dates, you could estimate year of conception and examine the data that way. This would be more appropriate analysis.

Response: Year of birth was used in an attempt to see whether the observed excesses in mortality were concentrated among persons born around the time of the peak releases from Hanford (i.e., 1945 and 1946). A number of analyses were repeated separately for the birth cohorts defined by the period 1940-44, and 1945-46 to reflect what might be reasonably assumed to be different exposure conditions. However, it is well recognized that this is a very crude approach to assessing exposure to Hanford radiation. It was not possible to conduct dose-response analyses based on individual estimates of exposure for persons who had died. Thus, the mortality analyses conducted using cause of death information were not capable of formally assessing the relationship between Hanford radiation exposure and outcomes such as congenital anomalies or pregnancy complications. The HTDS was not designed to evaluate mortality, and these analyses were never intended to investigate a relationship between Hanford radiation dose and cause of death among those in the cohort who died.

VII.8 Two findings of mortality analysis are especially notable: the excess in perinatal mortality and in fatal congenital anomalies, and the particularly high mortality among those born in Franklin County. To what extent do these overlap? i.e., Is the excess in Franklin County due to perinatal mortality? This should be addressed.

Response: As noted above in response to comment VII.7, the HTDS was not designed to evaluate mortality in this cohort. The study was not conducted in a manner that would allow for a detailed analysis of cause of death, or that would be capable of determining whether mortality in this cohort was associated with radiation exposure from Hanford. The primary purpose of reviewing death certificates for those who died was to determine whether any of the deaths were due to thyroid disease. The primary purpose of comparing the mortality experience in the HTDS cohort to that of the population of Washington State during the same time period was to see whether mortality in the HTDS cohort was substantially different (either higher or lower) than what might be expected based on the surrounding population. Extending the analyses to explore detailed patterns in specific subgroups of the population (e.g., those born in Franklin County and deaths due to specific causes) are not appropriate and are beyond the uses for which these data were intended.

VII.9 Mortality results should be discussed in the context of other relevant studies such as Sever et al. (Am J Epidemiol 1988; 127). Even though HTDS wasn't designed to explore mortality findings in detail, they deserve more consideration than is currently given on p.8 of Section IX.

Response: As noted in the responses above, the results of the mortality analyses conducted as part of the HTDS were not intended to address the same types of questions that studies like those of Sever et al were, and are not capable of doing so. Thus, direct comparisons of the HTDS mortality results are not appropriate. Nevertheless, in response to a number of comments and suggestions received after the release of the Draft Final Report, the mortality findings are

presented and discussed in considerably more detail in Appendix 23and section X..C.1 of the Final Report.

VII.10 The particular perinatal conditions and congenital defects should be described. This could prove informative, especially if coupled with data on place of birth and year of conception.

Response: This detailed information was not always available on the death certificate, and there were too few deaths from any specific cause to allow for a meaningful analysis. That is why such deaths were grouped into categories of similar causes. Further, as indicated above, this study was not designed to formally assess the relationship between Hanford radiation exposure and specific causes of death, nor was it capable of doing so.

VII.11 In terms of the excess in cardiovascular mortality, are there any obvious differences in risk factor prevalence that would explain it?

Response: Such an assessment is not possible, given the data available and thus is beyond the scope and capability of the HTDS.

VII.12 The SMRs were calculated using Washington State as the standard. Are there any regional data available that would provide a better comparison or are the statewide data correct?

Response: In conducting an analysis of this type, the most important consideration is whether the comparison population (and mortality rates used to calculate expected numbers of deaths) are truly comparable to the population under study (in this case the HTDS cohort). In addition, a practical limitation is often encountered in terms of the availability of the detailed data needed to perform the calculations. For the present analysis, it was necessary to have access to mortality rates by age, sex, race and geographic area over a period of approximately forty years or more by at least major category of cause of death. This dictated that we used statewide data. Such detail was not available from a smaller geographic region. In our judgment, the data for the State of Washington constituted the most comparable data available. Potential limitations of this approach are addressed further in the Discussion section.

VIII. COMMENTS REGARDING FINDINGS, INTERPRETATIONS, AND CONCLUSIONS

VIII.1 What is the "bottom line" of the study? What does it show?

VIII.2 The excerpt on page 7 [of Summary Report] states that 'the Director shall conduct a study of thyroid morbidity of the population.' A morbidity study determines the number of cases of a particular disease occurring in a given number of population. You chose to go further and add the objective of determining whether disease was increased. You should either not make that conclusion or should also address the other two possible conclusions of a morbidity study by also forming conclusions on whether there was no effect or that there was a decrease in disease as the radiation dose increases.

VIII.3 How can you explain away a problem that effects so many people - multiple family members with thyroid disease (no family history)?

VIII.4 Your findings basically say, hey if you "lived off the land" as our family did in North Idaho, you received no radiation-nothing to be concerned about. If you happen to have thyroid problems or any other problems health wise there is no way it could be tied to the Hanford releases.

VIII.5 What about long-term effects?

VIII.6 The Hanford Environmental Dose Reconstruction Project did not release their findings until April 21, 1994 and only then for representative doses, not individual doses. It is my opinion that chronic long-term exposure to Iodine 131 in the air, in the water, in the soil, in the food, in the milk, in whatever dose, resulted in thyroid disease.

VIII.7 I question why the study looked for a dose-related effect? The information I have from this population is that there is disease, with a wide variation in exposure and dose. Science may appreciate knowing how dose-response to disease was found by the Hanford Thyroid Disease Study. The Downwinders I have spoken with, know that the study does not reflect the disease they have experienced.

VIII.8 It is not possible to say that the thyroid disease in this population is not related to the Hanford emissions. There are health effects in this population that the design of the study does not address. The Downwinders are not reassured that the emissions from Hanford did not contribute to their thyroid disease. With all due respect to the researchers, the results of the Hanford Thyroid Disease Study are not conclusive, and do not accurately reflect the numbers of persons with thyroid disease and other diseases in the Hanford population.

VIII.9 .There should be discussion of: interpretation of the meaning of negative findings in an epidemiologic study

VIII.10 My wife, who was born in 1944 and was a downwinder, died in 1993. Of her graduating class (100 students) she was the 8th one to die of cancer…that is just not normal. Others in her family also have weak thyroids. I am troubled by the statement that there is no link, something must be wrong.

VIII.11 Are the researchers saying that 700,000 - 800,000 rads of I-131 is not harmful to the public?

Response: The HTDS was designed to determine whether exposure to atmospheric releases of primarily ^{131}I from the Hanford Nuclear Site between 1944 and 1957 resulted in increased thyroid disease among those exposed. The primary objective of the research was to describe in what way any increase in thyroid disease observed is related to the dose of radiation received; that is, to describe the characteristics of any dose-response relationship. This is the best way to assess whether exposure may have caused disease. The study was conducted as a long-term follow up study over a period of more than forty years after exposure. That was done to capture as much as possible any long-term or late effects of radiation exposure. The primary analysis utilized an

estimate of thyroid radiation dose for each individual based on information about their residence history and dietary consumption patterns during the times of the Hanford releases.

The overall ("bottom line") result is that this study found no evidence in any of the analyses that increasing dose to the thyroid from Hanford radiation was associated with an increased cumulative incidence of any of the disease outcomes or with increased prevalence of thyroid ultrasound-detected abnormalities, with results of thyroid laboratory tests, or hyperparathyroidism. These results remained the same when alternative methods of assessing radiation dose were used, and after accounting for uncertainty in dose estimation. There is no evidence that the absence of a dose-relationship was due to bias in selection of the cohort, loss to follow-up, or enrollment and participation.

Very important in the interpretation of these results is the assessment of the ability of the study to detect an increase in disease risk if it is present (i.e., the statistical power of the study). In order for the findings of a study showing an absence of an effect like that seen in this study (e.g., a negative study) to be very meaningful, there must be adequate statistical power to detect an effect of the magnitude that might be expected based on existing knowledge. The projections of study power, which were based on the results of the Pilot Study, were actually exceeded in the Full Study (as shown in Table IX.B-14 in section IX.B). Nevertheless, because uncertainties in the individual dose estimates could be expected to reduce study power, we undertook additional analyses to estimate the impact on study power of incorporating such uncertainties in the dose estimates. These new analyses are described in section IX.B.4. Although the effect of dose uncertainty was, as expected, to reduce the statistical power of the study, the reduction was modest. Even after accounting for uncertainty in doses, the HTDS had greater than 80% power to evaluate each of the hypotheses originally specified.

Given the principal differences between the radiation exposure circumstances at Hanford and those of other populations studied in relation to radiation-induced thyroid disease, the findings of this study are not inconsistent with the current published literature regarding the effect of exposure to radioactive iodine and the risk of thyroid and parathyroid disease. This is particularly so given the relatively small magnitude of the estimated thyroid radiation doses in members of the HTDS cohort (mean = 174 mGy) and the relatively protracted nature of the exposure over time. There is little evidence in the literature to suggest that persons exposed to radioactive iodine at the levels found in this study over a period of months or years would experience higher rates of thyroid or parathyroid disease as a result of their exposure.

This is not to say that there isn't thyroid disease in the population exposed to the Hanford radiation or in the HTDS cohort, or that exposure to radiation isn't harmful. The HTDS results show that thyroid disease is present in this cohort, and the results of the dose reconstruction project show that cohort members were exposed to Hanford radiation. It simply says that there is no evidence in this study of a link between exposure to Hanford radiation and the subsequent development of thyroid disease. This has raised a question for many of whether the study was incapable of finding that link because of the uncertain nature of the dose estimation used in the primary analyses and a concern that such uncertainty is so great that it renders the quantitative dose-response results inconclusive. The study has attempted to address this possibility in three ways. First, alternative qualitative methods of assigning exposure were used. Results from these analyses were consistent with those from the quantitative dose-response analyses. Second, two different approaches were employed to evaluate the impact of dose uncertainty on the primary risk estimates. Neither resulted in findings that were materially different from those ignoring such uncertainty. Third, the impact of dose uncertainty on study power was assessed using simulation methods. These analyses revealed that any reduction in statistical power due to uncertainty in

dose estimation was modest, and that even after accounting for such uncertainty the study had adequate statistical power to detect effects as small or smaller than those in the existing published literature.

Although any epidemiologic study is limited to some extent by uncertainty in the assessment of exposure, the impact of such uncertainty on the power of the study and the estimation of risk is seldom addressed to the extent attempted here. Further, the fact that epidemiologic investigations are inherently "uncertain" does not imply complete randomness or unpredictability, nor does it mean that reasonable conclusions cannot be drawn from such studies. Although these findings do not definitively rule out the possibility that Hanford radiation exposures are associated with an increase in one or more of the outcomes under investigation, the power of the study, even after accounting for the uncertainty of dose estimates, suggests that a failure to detect such an effect, even if it is very small, is unlikely.

VIII.12 I urge you to consider neck x-rays for people who were conceived in the Hanford area. There are many problems associated with the Klippel-Feil Syndrome–many are hidden symptoms because we do not communicate the symptoms. Since we are born with this problem many of the symptoms are normal to us, so we do not communicate them to a Doctor, until it is too late. Then we have paralysis, nerve problems, stenosis.

VIII.13 There are no comprehensive studies on the very specific area where it truly would have affected people– namely the unborn babies, and newborns of the workers at Hanford. (The workers took home a higher concentration of radioactive particles). They should be looking for spine deformities, mental retardation, and growth pattern problems specifically of the children of the workers of Hanford, or those conceived in the Hanford area.

VIII.14 M.S. is the highest in the nation in the beautiful Northwest, which is where Hanford Nuclear Reservation is located.

VIII.15 Health problems to Downwinders include chemicals, nuclear reactors and pesticides. Several relatives and neighbors are sick with various diseases including leukemia, MS and thyroid cancer.

VIII.16 Are other studies going to be done for other diseases?

Response: As described in section II.A of the Final Report, the HTDS was mandated and funded by Congress to specifically investigate whether thyroid disease was increased as a result of Hanford radiation releases from 1944-1957. Although we understand that there is considerable interest in studying the possible effects of Hanford exposures on diseases and conditions other than thyroid disease, such as multiple sclerosis, it was beyond the scope of the HTDS to do so.

VIII.17 I have followed the study with great interest particularly after I was diagnosed with papillary thyroid carcinoma in April 1998. My thyroid was located behind the sternum. Therefore the carcinoma had not shown up as a nodule in the neck during routine physicals.

VIII.18 Did the HTDS collect information about the location of the thyroid? Did such information show a greater incidence of carcinoma and other thyroid diseases? If so, I would like to see this information highlighted in the study or in a separate finding. Are there other studies that address the location of the thyroid?

Response: The HTDS did not collect information that would allow the investigators to distinguish anatomical differences in the location of the thyroid gland. Rarely, thyroid enlargement can occur in unusual locations (for example, behind the sternum). Most of these conditions are benign, although even more rarely it is possible for a thyroid cancer to occur there. However, in such instances a person would likely develop symptoms that would lead to medical care. Since we sought to obtain prior medical records for all participants reporting prior thyroid medical problems, it would be highly unlikely for such a condition to have been missed by the HTDS evaluation process.

IX. GENERAL COMMENTS AND COMMUNICATIONS

IX.1 I think my grandchildren are victims of Hanford. They have all kinds of cancer in their lives.

IX.2. Science is useless in solving social problems.

IX.3 The federal government conspired to eliminate liability for the releases.

IX.4 This study does not affirm my experience with the thousands of Downwinders with whom I have spoken who call the Network to talk about their thyroid and other diseases.

IX.5 No study has been done with a population exposed to constant radiation in varying amounts over a long period of time. Neither has there been a study that can account for each individual response to a stimulus.

IX.6 There is no consideration for political context in the study. The DOE and the US Government are political entities, and they could not do a scientific study - they could get a technological answer, but not a scientific one.

IX.7 .The Green Run of December 2, 1949 was an immoral act and yet the government has never apologized.

IX.8 There was no provision in the study to cover lost wages during the testing. I just couldn't afford to take off from work.

IX.9 The thought of government people chopping pieces off my thyroid sent a cold chill up my spine.

IX.10 Request that the FHCRC publicly retract the statement: "These results provide rather strong evidence that exposures at these levels to I-131 do not increase the risk of thyroid disease or hypoparathyroidism. These results should consequently provide a

substantial degree of reassurance to the population exposed to Hanford radiation that the exposures are not likely to have affected their thyroid or parathyroid health."

IX.11 The HTDS lacks humanity and compassion.

IX.12 The HTDS has effects on emotions and litigation. We (the HTDS) doesn't recognize this.

IX.13 Given the following quote, how could you justify releasing the HTDS draft report when you knew that not all of the final analysis plan had been completed, namely the incorporation of the dose uncertainty into the dose-response analysis? The Study Management Team (SMT) "consider that incorporating the adjustment for dose uncertainty is an essential requirement for the study. That this is indeed a matter of practical importance can be seen from the results of the Utah thyroid study, in which the magnitude of the estimated dose response was roughly tripled by the adjustment for dose uncertainty." The quote appears on page10 of the attachment to the 06/30/97 analysis plan. The attachment is titled "Hanford Thyroid Disease Study Analysis Plan: Summary of Revisions of 1/27/97 Draft, June 30, 1997.

IX.14 Both CDC and the Fred Hutchinson Cancer Research Center (FHCRC) should offer a prominent public apology for their inappropriate characterizations of the power of the study's conclusions during the January 1999 briefings and announcement (see previous comment).

IX.15 The public impact aspects (the way the HTDS results were released) need to be included in their report. Prior to the results on January 28, 1999, I and the media and Congress were completely shut out.

IX.16 The researchers are not dealing with how the report affected the public, that they were ignoring that aspect of their responsibility to handle the social side of releasing the report.

Response: A number of comments such as those above have made it clear that some individuals believe strongly that Hanford radiation emissions have caused their own thyroid or other health problems, or are responsible for a variety of health conditions in friends or relatives. These beliefs are not based on the results or conclusions that have arisen from any scientific or medical studies, but rather are based on personal experience and perception. A number of these comments go on to criticize the HTDS study team for not being sensitive to their health problems or their concerns about the effects of being exposed to radiation from Hanford, and to the way the draft results of the study were communicated to the public.

We understand that it is difficult to accept the results of this study under such circumstances. We respect the rights of all individuals to hold and voice their own opinions and beliefs in this regard, even when those beliefs may not necessarily be based on objective or scientific results. In the same spirit, it is important for members of the public to understand that the primary responsibility of the HTDS team has been to conduct the very best scientific study possible, using the most rigorous scientific methods available. We have been uncompromising in attempting to uphold the very highest standards of excellence in all aspects of the project, and to conduct the study in an unbiased and neutral manner. To help us in this process, we have sought and received extensive

feedback from scientific peers, the federal HTDS Advisory Committee, CDC staff and consultants, and the public in each stage of the study.

Thus, even though the results may be different from what some feel they should be, and no single epidemiologic study ever provides an answer with 100% certainty, we believe we have provided the public with the best possible answer that science could provide to answer this specific question, and have done so in a scientifically rigorous and unbiased manner. Accordingly, we believe it was important to present these findings in a straightforward way, and to provide our best assessment of what they mean and our confidence in them. It is regrettable that this approach was interpreted by some to indicate a disregard on our part for individual circumstances and a lack of compassion and humanity. That was never the intent. We fully realize the potential impact of these findings on individuals, and believe that one of the best ways to show compassion under such circumstances is to deliver the very best scientific product possible.