ORHASP: FEASIBILITY OF EPIDEMIOLOGIC STUDIES

FINAL REPORT

EXECUTIVE SUMMARY

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EXECUTIVE SUMMARY

1. Background

In September 1942, the U.S. Federal Government established the Oak Ridge Reservation (ORR) in a remote farming community in eastern Tennessee for the production of fissionable materials for building nuclear weapons as part of the Manhattan Project. The ORR included three main facilities: the Oak Ridge Gaseous Diffusion Plant (code named K-25) for production of enriched ('bomb grade') uranium through a gaseous diffusion process; the Y-12 facility for production of enriched uranium through an electromagnetic separation process; and the X-10 facility (now called the Oak Ridge National Laboratory [ORNL]) with a graphite reactor for producing plutonium and a chemical separations plant. After the War, the ORR continued to play a major role in the U.S. nuclear weapons program, but in addition significantly expanded its mission to include basic and applied research for peacetime use of nuclear energy.

During the past fifty years, production, research, and waste disposal operations at all three of these facilities have resulted in inadvertent releases of hazardous and radioactive wastes to the environment (outside the ORR). These releases have impacted the environment by contaminating the surrounding air, soils, sediments, vegetation, animals, ground water, and surface water. Depending on their physical and chemical properties, some of the materials have persisted longer than others in the environment. Thus, the human population living in the area may thus have been or continue to be exposed through these pathways with increased risks to their health.

The Tennessee Department of Health (TDH) and the United States Department of Energy (DOE) signed an agreement in 1990, called the Oak Ridge Health Studies Agreement. In this agreement, the DOE would provide funding to the State for coordinating independent health-related studies to evaluate the potential health risks to off-site populations possibly exposed to hazardous materials from past and present ORR operations. An independent panel called the Oak Ridge Health Agreement Steering Panel (ORHASP) was set up to advise and provide direction to the study. In addition to the main Dose Reconstruction Study, ORHASP also recognized the need to directly evaluate health outcomes, utilizing findings of the dose reconstruction study to define exposure. Thus, ORHASP commissioned investigators from the Department of Preventive Medicine at Vanderbilt University to explore the feasibility of initiating meaningful, valid epidemiologic studies to address potential health concerns in the off-site population of the ORR.

The main objectives of the study were 1) to review four priority contaminants (iodine-131, cesium-137 and other radionuclides, mercury, and polychlorinated biphenyls) identified from the Phase I Dose Reconstruction Feasibility Study, 2) to review health outcomes of concern associated with these contaminants, 3) to review data needs for an epidemiologic study and describe sources and availability of such data in Tennessee, and 4) to develop guidelines for determining the need for an epidemiologic study. In addition, the investigators would provide

general epidemiologic support to ORHASP, and meet with individuals and community groups as needed. This report describes the findings of this study.

The city of Oak Ridge and the DOE ORR are located 40 km to the west of Knoxville, Tennessee. The ORR is located within the corporate city limits of the City of Oak Ridge, in Roane and Anderson counties, in eastern Tennessee. It consists of approximately 35,236 acres of federally owned lands, and is bounded on the north and east by the populated portion of the City of Oak Ridge and on the south and west by the Clinch River.

2. Rationale for Epidemiologic Studies

There are several reasons why a health effects study could be undertaken. First, in an open, democratic society, citizens have a right to know whether some activities undertaken by their government, whether in the past or the present, have in any way increased the risk to their health or adversely affected it. Knowledge gives members of a community the means to deal with such true or perceived health risks, regardless of when the exposure may have occurred. Second, it is important to know whether there are current hazards that might adversely affect public health. If there are, appropriate actions can be taken to minimize health risk to the public. Third, a health effects study may identify evolving health problems associated with exposure to hazardous materials in the past. In such instances, exposed individuals could be screened for early detection and treatment of disease, and also for medical follow-up, if needed. Finally, a health effects study could be done primarily for advancing scientific knowledge and understanding of whether a contaminant has any adverse health effects.

3. Epidemiologic Designs

Epidemiology is defined as the study of the distribution and determinants of diseases and injuries in the human population. Although there are several epidemiologic study designs, they can be broadly classified into two types, descriptive and analytic. Descriptive studies (case series, cross-sectional, ecologic studies) are generally useful for generating hypothesis (i.e., providing direction for future research) but not for establishing causal inferences. Analytic studies (cohort and case control studies), on the other hand, are used for studying the etiology (risk factors) of disease to provide evidence for establishing causal inference. A brief description of cohort, case-control, case series, cross-sectional and ecologic studies is presented next.

Cohort Study. In a cohort study, groups of subjects with and without the exposure of interest are identified. The cohort usually is free at baseline of the disease under study. The groups are then followed over time to ascertain outcomes (disease or end point) and rates between the two groups are compared. Depending on the timing of disease (outcome) occurrence, cohort studies are classified as *prospective or retrospective (or historical)*. In a prospective study, the cohort is assembled at the beginning of the study and then followed into the

future for any occurrence of disease. A retrospective cohort study is different from the prospective cohort design in that the disease (end point) being studied has already occurred and the follow-up period is complete when the study begins. The cohort of disease-free individuals with (and without) the study exposure is identified historically, usually with the help of existing records. A major advantage of this design is that while it retains the major strengths of the prospective design, it can be done quickly with less resources. However, a serious limitation of the retrospective design is its reliance on the availability of reliable and valid records in defining exposure, measurement of confounder and ascertainment of disease occurring in the past. Nevertheless, it is widely used in epidemiologic studies of occupational exposures.

Cohort studies minimize bias in ascertainment of exposure if prospective, allow direct measurement of incidence of disease in exposed and unexposed groups, and can examine multiple diseases (outcomes) associated with a single exposure. However, they are inefficient for rare exposures, can be expensive and time consuming if prospective, and validity of results can be seriously affected by losses to follow-up.

Case Control Study. In a case-control study, groups of subjects with (cases) and without (controls) the disease of interest are identified and then the frequency of their exposure prior to disease onset in cases and for a comparable time in controls is determined. Case control studies are relatively cheap, quick and very efficient for study of rare diseases, and multiple exposures can be studied for a disease. However, a major limitation of this design is its vulnerability to bias in exposure ascertainment. An increasingly popular variant of a case-control study is called the *nested case control study*. This is really a case control study within a retrospective or prospective cohort study. In a nested case control study, members of a specified cohort who develop the disease (cases) of interest after a specified follow-up period are first identified. A sample of cohort members who have not developed the disease (controls) is then selected. The frequency of exposure in cases is compared to the frequency in controls, similar to a case control study. A major advantage of this design is that while retaining the strengths of a cohort study, it significantly reduces the size and cost of the study and increases its efficiency.

Case Series Study. The case-series study is a case control study without the controls. It is particularly useful for identifying potential problems meriting further investigation. However, without a control group, it is generally difficult to determine whether or not exposure frequency in the cases is different from that expected by chance, unless the outcome is distinctive and is closely linked temporally with the exposure of interest (e.g., use of thalidomide by pregnant mothers and infants with deformed limbs).

Cross-sectional Study. In a cross-sectional study, exposure and disease status are ascertained at a single point in time. Such cross-sectional studies are particularly easy to conduct because all variables are ascertained at a single time, the present. However, this design has two major limitations. First, the temporal sequence is unknown, thus, exposure may follow rather than precede disease. Second, because the disease cases are prevalent (i.e. new and old cases), the

association with exposure is influenced by survival.

Ecological (Correlational) Study. In an ecological study, both exposure and disease rates are determined for large groups of subjects without knowledge of exposure and disease status of individuals. Thus in such a study, the unit of analysis is a population. Very commonly these studies involve comparisons between geographically distinct populations (for example, comparisons of cancer mortality between different geographic areas). Studies of cancer mortality in populations living near nuclear facilities have generally been ecologic ones. Cancer mortality rates in these areas are compared to rates in other geographic areas without nuclear facilities or with the national U.S. rates. These studies are relatively easy to conduct because of availability of data. There are 3 major problems with ecological studies for diseases with multiple risk factors. First is the "ecological fallacy" (defined as inappropriate conclusions regarding relationships at the individual level based on ecological data); those who died of cancer in areas near the vicinity of nuclear facilities may have moved into the area recently and thus would not have had adequate time to have been 'exposed' and develop cancer. Second, is the cross-sectional nature of the analysis; one does not know whether 'exposure' precedes or follows the development of cancer. Finally, it is difficult to control for other potential causes of cancer.

Preferred Design. In addition to the relative merits of individual study designs, important factors influencing choice of study include specification of the primary purpose of the study, availability of data and operations (logistics). In the Oak Ridge setting, the period of highest releases of contaminants appears to have occurred over three decades ago. Thus, a sufficient time interval has elapsed for possible manifestation of endpoints, including diseases with long latent periods, such as cancer. If a cohort of individuals from this time period whose exposure status can be measured is specified and followed-up to the present to ascertain the presence of endpoints, a retrospective cohort study could be done. Thus, for studies of health effects associated with past exposures, a retrospective cohort study would be the design of choice. On the other hand, for studies of future effects associated with current levels of exposure (likely to be much lower than past levels in the Oak Ridge setting), either a prospective cohort or a nested case control study would be designs of choice.

4. Requirements for a Valid Cohort Study

The requirements for a valid cohort study include specification of the cohort, definition and measurement of exposure, measurement of confounders, ascertainment of disease (outcome), and adequate sample size for analysis.

Specification of Cohort. The population (cohort) to be studied needs to clearly specified. A primary issue in selection of the cohort is the tradeoff between the need to identify persons willing to participate and capable of providing good data and in whom there is a reasonable likelihood of detecting an effect (internal validity) versus the need to have a representative sample

of the exposed population (generalizability). Once specified, all members of the cohort should be followed. If cohort members are lost to follow up, then rates of loss may be associated with exposure status (e.g., radiation exposure). Such differential loss to follow-up can introduce selection bias.

Measurement of Exposure. Accurate measurement of exposure is crucial for any epidemiologic study. If subjects are inaccurately classified by their exposure status at baseline (misclassification) or if the status changes (e.g., a study of smokers where some quit smoking during follow-up), then the ability to find a true association is reduced. This is a common problem in studies of populations living near nuclear facilities, where geographic distance is used as a surrogate for exposure to radiation.

Measurement of Confounding. Confounding is "the distortion of a disease/exposure association brought about by the association of other factors with both disease and exposure". For confounding to be present, the confounder must itself be a risk factor for the disease (or serves as a proxy measure for unknown or unmeasured causes) and must also be associated with the exposure in the cohort or study base. For example, in cohort studies of lung cancer and uranium miners, smoking is an important confounder because smoking is not only a predictor of lung cancer but it is also related to the life style of miners.

Ascertainment of Disease. It is important that *all* members of the cohort who develop disease are identified *accurately*. Misclassification of disease-free persons occurs when the method used to ascertain disease (or identify cases) incorrectly includes persons without disease. This is a failure of the method's *specificity* because it cannot correctly identify disease-free persons. If this misclassification is random, its effect will be to reduce relative risk. If this misclassification is differential, bias may be introduced. On the other hand, incomplete identification of persons with disease also results in misclassification. This occurs when the method used to ascertain disease (or identify cases) have poor *sensitivity* or there is incomplete identification of all cases of disease occurrence in the cohort. In cohort studies, the primary reasons for missing cases are 1) incomplete follow up, missing disease that occurs after a cohort member is lost to follow up, and 2) insensitive procedures for case identification.

Sample Size. A major problem of cohort studies (indeed all studies), particularly prospective studies, is adequate sample size. Generally, given a fixed power (80%) and a level of significancer (alpha of 0.5), the sample size required is a function of the disease rate in the general population (background rate) and the minimum detectable risk desired. For example, for a study in which the rate of disease is 10 per 100 and a detectable relative risk of 1.5 (i.e., a 50% increase in risk) is desired, 1000 exposed and 1000 unexposed subjects would have to be studied. On the other hand, if the disease rate were 1 per 100,000, millions of subjects would have to be studied, given the same relative risk. Large studies of this type are very expensive and time-consuming. Thus, it is particularly important to perform careful power calculations when designing a cohort

study.

5. Requirements for a Valid Case-Control Study

The requirements for a valid case control study include specification of the study base, disease (case) ascertainment, control selection, definition and measurement of exposure, measurement of confounders, and adequate sample size for analysis.

Specification of Study Base. The cohort underlying a case-control study is called the *study base*, defined as the population giving rise to the cases or persons who would have become cases had they developed the disease.

Two basic assumptions of a case-control study are that 1) an underlying cohort (well defined population), from which the cases arise, can be identified; and 2) the controls are a random (possibly stratified) sample of this cohort. If we further assume the disease is rare (<10% rate), and if information is collected from subjects in the same way, case-control studies satisfying 1-2 above are inferentially equivalent to cohort studies; the former samples the non-case population to improve efficiency. Although not made explicit in the above derivation, it also is assumed that exposure can be measured with equal accuracy before (cohort) or after (case-control) the disease has occurred. In many studies, this assumption may be difficult to satisfy.

Disease Ascertainment. Just as in a cohort study, cases of disease (or a defined random sample) occurring in the study base need to be ascertained with high specificity and sensitivity. Failure to do so will cause the same errors of misclassification and selection bias as occur in cohort studies. Cases should generally be restricted to those newly developing the disease (incident cases); otherwise one is also studying factors associated with survival. In addition to inclusion of only confirmed cases, the time of disease onset needs to be established. Other study variables need to be collected for a time prior to disease onset.

Control Selection. Ideally, controls must be selected from the same population that the cases arose from, i.e. the controls should be a random sample of the study base, and should also be comparable to the cases in terms of their risk of developing the disease (e.g., in a study of estrogens and ovarian cancer, women with no ovaries would be inappropriate to serve as controls since they are not at risk of developing ovarian cancer.) In other words, the controls must be representative of those subjects, who had they been ill, would have become cases.

There are several options for selecting controls, including random sampling, random digit dialing (telephone), neighborhood controls, hospital controls, and friend/relative. The preferred options are random sampling from a primary study base with a roster (e.g., from birth certificates for a county during a given year), or in the absence of a roster, neighborhood controls. Other options have many problems.

Measurement of Exposure. The same issues of definition and measurement in cohort studies are present in case-control studies. For this design, the most common method of exposure ascertainment is subject interview. This, in conjunction with the case-control design, poses several potentially difficult problems. First, needing to complete an interview may reduce participation rates, possibly differentially between cases and controls. Nonparticipating subjects may introduce potential selection bias. Second, obtaining accurate information on past and present exposure status may be difficult. Often, interviews are conducted after the exposure period of interest. Subjects may be interviewed well after disease onset and there is possibility of differential recall of past exposures (recall bias). Finally, obtaining information of equal accuracy from cases and controls is also a problem.

Confounders. Again, a unique problem for case-control studies is that subjects are entered into the study after the disease has occurred, whereas pre-disease data on confounders are needed. Often, data on potential confounders are collected from subject interviews.

Sample Size. The issues of sample size are similar to cohort studies (see previous section), but in general, the sample size required in case-control studies is smaller. It is important to determine the sample size required to detect the association that one is evaluating with adequate statistical power.

6. Inventory of Data Resources for Epidemiologic Studies in Oak Ridge, Tennessee

A central question in all types of epidemiologic studies is where and how to obtain the data needed to define exposure and confounders and to ascertain disease occurrence. Regardless of study design, valid results will depend upon accurate data collection. There are two broad classes of data: a) those obtained directly from the subjects for the purposes of the study and b) those obtained from records collected for other reasons (e.g. birth and death certificates, occupational records). The appropriate sources of data depend almost entirely upon a study's objectives and resources. Very often, multiple sources are appropriate (i.e. data are collected from the subjects and also from records).

Data Collection from Subjects. Keeping the potential disadvantages in mind, all the data needed for an epidemiologic study (for defining exposure, ascertaining disease, and identifying confounders) can be collected directly from subjects. There are many methods for data collection from subjects. Some of these include personal interviews (e.g., history of exposure to certain chemicals, smoking, residence history, disease), structured assessments (e.g., developmental scales for infants), physical examination (e.g., blood pressure), biochemical measurements (e.g., levels of chemicals in blood), and examination of the environment (radon level in a subject's house).

Data Collection from Existing records. In epidemiologic studies, existing records (automated or manual) can be used to define a study population (e.g. births in a defined area and time), to measure exposure (e.g. medication use from Medicaid pharmacy files, workers exposed to ionizing radiation from occupational records), to ascertain disease (e.g. cancer registry, death certificates), and to trace/locate study subjects (e.g. marriage and divorce certificates, driver license files).

Record sources that may be of potential use for future epidemiologic studies in the Oak Ridge include 1) databases of records routinely collected and maintained by the Tennessee State Department of Health and other agencies, 2) databases in the Department of Preventive Medicine at Vanderbilt University, 3) health care provider records (hospital and physician records), and 4) miscellaneous, including national and local databases.

Birth Certificates. In Tennessee, birth certificates have been recorded and filed since 1914, but are available in a computerized format from 1959 to the present. Demographic data about the mother, child, and father contained in the birth certificate are useful for tracing individuals and also for serving as the basis in selecting population controls for epidemiologic studies. However, the quality of data recorded in the birth certificate varies with different data items. For example, birth weight is generally accurately and consistently recorded; gestational age on the other hand is very subjective and not clearly recorded.

Death Certificates. In Tennessee, death certificates have been recorded and filed since 1914, but are available in computerized format from 1949 onwards. Because demographic characteristics of the deceased subjects (namely their name, address, age and gender, and the underlying cause of death) are recorded in the death certificate, it serves as the basic document for all mortality data. The underlying cause of death is a very useful data item for enumerating cause of mortality in a given population by different personal characteristics. The usefulness of death certificate data as an indicator of disease frequency in a population varies largely on the disease being studied. Diseases with high case fatality rates, those that are rapidly fatal and those that are relatively easily diagnosed are most likely to be recorded accurately on a death certificate as an underlying cause of death. Other problems associated with mortality data being used for epidemiologic purposes include variable quality and/or careless certification of cause of death (e.g., in rural areas with few physicians, death may be certified by a coroner), incorrect assignment of cause of death codes and changes in rules for assigning these codes over time.

Tennessee Cancer Reporting System. The TCRS was set up following legislation in 1983 that made cancer a reportable disease in Tennessee. Tennessee hospitals and laboratories that diagnose and/or treat cancer are to the report cases to the Department of Health. Hospitals are required to the report information regarding each patient seen for cancer diagnosis and/or cancer-directed treatment to the TCRS using a standard abstract form. Hospitals are required to submit reports, quarterly, even if they did not see any cases. All cancers, regardless of method of confirmation, are reportable. Although the TCRS started collecting data on cases diagnosed after

January 1, 1986, compliance in reporting has improved since 1989. The TCRS already is and will be an invaluable resource for measuring cancer incidence and monitoring for unusual trends and patterns for the population in Tennessee, and for generating hypotheses for epidemiologic studies. It will be an excellent source for case ascertainment and for determining cancer endpoints in specific epidemiologic studies.

The Hospital Cost Containment Information System. The Hospital Cost Containment Information System has been collecting data, primarily to be able to compare and monitor charges among Tennessee hospitals, reported to the State by private third party payers. However, effective 1994, data from Medicaid and Medicare and also private payors will be included. The data are recorded on claims froms for services provided by Tennessee hospitals, and cover all paid inpatient and outpatient claims. Although the first computerized data processed were for calendar year 1990, reliable data are available from 1992. These data could be an invaluable asset for epidemiologic studies if individuals with a given disease could be identified and then, by using the patient control number, their medical records accessed for verification of demographic and diagnostic data.

The Tennessee Birth Defects Registry. The Tennessee Birth Defects Registry is a population-based, statewide registry covering birth defects occurring to infants of residents of the State in a given year. The surveillance system is a passive one which relies on existing databases in the Tennessee Department of Health to identify cases of birth defects. All cases identified from these databases are verified prior to inclusion in the Registry. The first year of data includes infants born to Tennessee residents during 1991. The goals of the Registry are monitoring birth defects to detect changes or unusual patterns in incidence that may suggest an environmental influence, developing hypotheses for analytical epidemiological studies related to birth defects, and planning and evaluating services available to infants and parents of infants with birth defects.

Marriage/Divorce Registration. All marriages and annulment of marriages in Tennessee must be registered. The certificates contain demographic data on the individuals, such as name, date of birth, gender and address. This is a useful source of data for tracing or locating subjects and also by helping to identify changes in surnames of women.

Vehicle Registration/Drivers License. Since 1984 the Tennessee Department of Transportation and Safety has computerized records of all vehicles that are registered in the state and also of all licensed drivers. These files contain demographic characteristics of individuals, specifically their name, gender, date of birth, and residence. These records are very useful in tracing and identifying subjects, since most adults have registered vehicles and/or drivers license.

Automated Databases at Vanderbilt University. Automated databases, such as Tennessee Medicaid, arise from systems for providing medical care for defined populations. For administrative or medical records reasons, records of encounters between patients and health care

providers are kept. Using Tennessee Medicaid files from 1975 onward and linking with other Vital Statistics files (birth, death, fetal death files), the Department of Preventive Medicine at Vanderbilt University has set up and maintains a unique record-based system which has the potential capacity to support entire epidemiologic studies, providing data on exposure (such as drugs) and outcomes (illness), and on some confounding variables. However, the greatest limitation of these databases in the Oak Ridge setting is that they are not available for the periods when the effects of the highest public exposures are most likely to be found.

Medicaid enrollees are not a random sample of or even a representative selection of the U.S. population. Indeed, it is helpful to think of Medicaid as distinct populations: 1) pregnant women, 2) infants and children, 3) young mothers, 4) disabled and blind, and 5) the aged. Table 10.3.1 illustrates this point, showing how the Tennessee Medicaid population differs from that of the state. Thus, Medicaid is particularly well suited to study infants, the elderly, persons in nursing homes, and African-Americans. Conversely, Medicaid is poorly suited for study of some populations, such as middle aged males.

Tennessee Childhood Cancer Database. The Department of Preventive Medicine at Vanderbilt University has set up a TN childhood cancer database for children born on or after January 1, 1975 in Tennessee. The database is limited to children born after January 1, 1975. The database currently includes all cases of childhood cancer first diagnosed between January 1, 1975 and December 31, 1992 in Tennessee and were born in Tennessee (i.e., linked to a Tennessee birth certificate). Data elements in the database include child and parent's names and address, demographic information (date of birth, gender, state of birth), date of diagnosis and institution making the diagnosis, and cancer type. In the Oak Ridge setting, this database would thus be useful in studies trying to identify cancer cases in children born in this area (county of birth) from 1975 through 1992. Furthermore, this database can be continually updated with data from the TN Cancer Registry, thus increasing its value in the coming years.

Hospital Records. Use of hospital records to obtain information on disease occurrence with few exceptions requires reviewing the medical records and abstracting data items that are relevant for the disease under consideration. Hospital records usually have good diagnostic information, and are useful for studying diseases that are traditionally treated in hospitals. In an informal survey of hospital medical records staff in Roane and Anderson counties and fourteen surrounding counties, only 3 of 22 hospitals had a computerized disease retrieval system using ICD diagnostic codes prior to 1985, and 18 of the 22 after 1985. Prior to computerization, identification of patients by disease could be done by manual review of index cards, microfiche/microfilm, or actual medical records. However, the period of availability of such records varied considerably by hospital. For example, Ft. Sanders Loudon Medical Center had microfiche/microfilm records available from 1939 whereas Athens Community Hospital had records from 1981 onward. Methodist Medical Center in Oak Ridge had microfiche/microfilm available from 1972 onward. Although the hospital had some records dating back to the early

years of its establishment as a Military Hospital, these records were mainly limited to patients who received care after 1972. However, the major hospitals in Knox County had records dating back to the 1950s or the years they were established. These findings indicate that for epidemiologic studies, case ascertainment for illness diagnosed prior to 1985 is feasible though labor intensive. The likelihood of missing records is also of concern, raising issues of possible bias due to underascertainment of cases.

Physician Records. Records of physicians in office-based or group practice may appear to be a valuable source of data for ascertaining diseases, especially for diseases treated in physician offices only. Obtaining permission for these records is usually very difficult due to privacy and confidentiality reasons. Furthermore, physician records are usually brief, providing limited information on primary symptoms and basic diagnosis and laboratory data and primary diagnoses. However, for certain diseases (e.g., ALS), which are seen primarily or through referral by specialty physicians (i.e. neurologists for ALS), surveying records of such physicians may be useful. However, because of physician attrition from a given area due to retirement, death, and relocation, physician records are of limited use for ascertaining diseases diagnosed in the distant past.

Conclusions. The inventory of data sources reviewed suggest that data needed for an analytic epidemiologic study in the Oak Ridge population are potentially available. Data needed for identifying the population potentially exposed historically to one or more of the contaminants of concern could be available from the current Dose Reconstruction Study. Sampling, tracing and/or locating such individuals can be done using the sources described above, such as use of birth and death certificates, marriage and divorce records, drivers license and vehicle registration records, old telephone directories and current CD-rom telephone directories. Dose estimates to individuals could be calculated with additional information obtained from interview questionnaires. Outcomes can be ascertained directly from subject interview and/or physical examination, review of medical records in hospitals, and death certificates. Automated disease registries, such as the TCRS, the Birth Defects Registry, and the Vanderbilt databases, can be useful sources in screening for potential study subjects who may have been diagnosed with a study disease. However, a major limitation of these registries is that they were established only recently. Thus, they lack data for the period (1950s - 1960s) during which the population was at the highest risk for exposure to the contaminants. Similarly, the completeness and quality of medical records in hospitals of this region for the earlier time period appear to vary by institution. Well defined outcomes, such as cancer, would be easier to ascertain than ill defined ones, such as tremors or neurological deficits. If an epidemiologic study were considered in this population in the future, a pilot phase to evaluate availability and quality of data needed for the specific study should be conducted prior to the main study. Nevertheless, any meaningful study would face considerable logistic challenges and require substantial resources and time to implement.

7. Iodine-131

Iodine-131 is a short-lived (radioactive half-life of 8.4 days) product of nuclear fission emitting mainly beta and gamma rays. From 1944-1956, as a result of the radioactive lanthanum (RaLa) processing in the X-10 Plant of the ORR, upto 300,000 curies of ^{131}I is estimated to have been released, mainly to the atmosphere, as reported in the findings of the Phase I Dose Reconstruction Feasibility Study (Phase I). The off-site population living downwind (within 20 km of X-10) could have been exposed by inhaling the ^{131}I or by ingesting contaminated foods (especially fresh milk and vegetables). However, infants and children who drank fresh milk from cows and goats grazing in open pasture would be at risk of higher exposures. Because of its short half-life, it is not present in the environment at the present time.

Because iodine is selectively concentrated and stored in the thyroid gland, the main health outcome of concern from exposure to ^{131}I is thyroid disease, including neoplasms (benign and malignant) and hypothyrpidism. The type and frequency of thyroid disease associated with radiation depends on several factors, including type of radiation, dose, dose rate, age at exposure, current age, and gender. At high external doses (>1500 rad), thyroid cells are ablated, thus predisposing to hypothyroidism. At lower doses, carcinogenesis predominates. The thyroid gland can be exposed to external photon (gamma or x-radiation) or internal radiation from beta-emitting radioiodine deposited in the thyroid gland.

Thyroid Neoplasia-External Gamma Radiation. Evidence linking ionizing radiation with the development of thyroid neoplasms in humans has come from studies of persons who were previously exposed to therapeutic external gamma radiation in childhood, primarily for benign head and neck diseases and from studies of Japanese A-bomb survivors who were exposed primarily to external gamma radiation.

Follow-up studies of several cohorts exposed in childhood to external gamma radiation and evaluated for the subsequent development of thyroid neoplasia collectively demonstrate a dose-response relationship between gamma radiation dose and the development of benign thyroid adenomas and thyroid carcinomas. The range of mean doses evaluated has been between approximately 6 and 808 rad to the thyroid. Estimates of absolute excess risk per million person-year-rad (PYR) range from 0 to approximately 4, averaging about 2.5 per million PYR. Among people exposed in childhood to external gamma radiation, the absolute risk for total thyroid nodules, including cancer, has been reported to be 12.3 excess cases per million PYR. Studies of Japanese A-bomb survivors exposed primarily to gamma radiation show a similar dose-response relationship for thyroid nodules. Women and those who were of young age at exposure had significantly higher prevalence rates.

Thyroid Neoplasia-Exposure to Internally Deposited Radioactive Iodine. Although animal studies clearly indicate that internal doses of ^{131}I can induce thyroid neoplasm, this relationship is less clear in humans. Radiation doses from internally deposited ^{131}I is estimated to be one-third to two-thirds as effective as external photon irradiation. The principal sources of

evidence from human populations include studies of 1) persons receiving therapeutic (high) doses of ^{131}I for Graves' disease or thyrotoxicosis and persons receiving diagnostic (lower) doses for suspected thyroid disease, and 2) populations exposed to radioiodine from radioactive fallout in the Marshall Islands and Southwestern Utah. In the former, there is no overall convincing evidence that the risk of thyroid neoplasm is increased among persons receiving therapeutic doses of ^{131}I.

Studies of residents of southwestern Utah who had been exposed as children to ^{131}I from radioactive fallout from nuclear testing in the Nevada Test Site between 1951 and 1958 have suggested up to a 30% excess of all types of thyroid abnormalities among the exposed group. Although limited by the small number of exposed individuals and low incidence of thyroid neoplasms, a recent study of this cohort where individual doses were estimated (range of doses 0-460 rad) demonstrated a statistically significant excess of thyroid neoplasms (benign and malignant; n=19), with an increase in excess relative risk of 0.7% per milligray. Malignant neoplasms, when considered alone, were not significantly elevated. Although limited by lack of precise dosimetry, studies of the Marshall Islanders, who were exposed to radioactive iodines from nuclear fallout during atmospheric testing, suggest that persons exposed to mixed radioactive iodines are at a much higher risk for developing thyroid morbidity and that the prevalence of both benign and malignant thyroid nodules all increase with dose.

Hypothyroidism. It is estimated that ionizing radiation at external doses above 1500 rad may cause enough damage to the thyroid to produce hypofunction of the gland and permanent hypothyroidism, although lower doses may produce partial hypothyroidism. Studies of persons treated with high doses of ^{131}I for Graves' hyperthyroidism demonstrated a strong linear dose-response in the development of hypothyroidism. The data indicate that approximately 15% of persons exposed would develop hypothyroidism within five years of exposure. Hypothyroidism has also been reported in studies of A-bomb survivors in Japan.

8. Cesium-137 and Other Radionuclides

In Oak Ridge, ^{137}Cs together with several other radionuclides, mostly products of nuclear fission, such as cesium-137, ruthenium-106, strontium-90, were released to White Oak Creek to the Clinch River and the portion of the Tennessee River above the Watts Bar Dam from early 1944 through the early 1960s. Although the magnitude of releases is unknown, existing data suggests the total is orders of magnitude less than the total ^{131}I releases. The primary pathways of human exposure are expected to be consumption of aquatic biota in the Clinch and Tennessee Rivers, use of contaminated water for drinking, direct exposure to shoreline sediments, and consumption of agricultural produce grown on soils contaminated through irrigation or dredging of sediment. Because these radionuclides, with the exception of ruthenium-106, have long half-lives, they persist in the environment for many years. Individuals could thus be exposed to these contaminants via ingestion of contaminated food/water or via external sources. The exposures could have led to doses to a variety of organs and the "whole body" and such exposures may

increase the risk of cancer and other health effects.

Adverse Health Effects of Ionizing Radiation. Ionizing radiation and its effect on human health has been extensively studied over the past few decades. Although the adverse health effects associated with exposure to high doses of ionizing radiation are well established, they are not as well documented for exposure to low doses (the magnitude of exposure that might be expected to occur in the general population living near nuclear facilities). Thus, data from the higher dose studies have been extrapolated to estimate risk at the lower levels of exposure, especially with regards to its carcinogenic and genetic effects. However, the appropriateness of this is an ongoing controversy in the radiation health field. The *Committee on the Biological Effects of Ionizing Radiations-BEIR V Report* and the *UNSCEAR Sources, Effects and Risks of Ionizing Radiation Report* have extensively reviewed the health effects of low levels of ionizing radiation.

Much of the human data has been obtained from findings of studies of several cohorts of individuals who had been exposed to relatively high doses of radiation. These include 1) atomic bombings of Hiroshima and Nagasaki, 2) diagnostic and/therapeutic irradiation for medical conditions, 3) occupation (luminous dial painters, uranium miners, radiologists, nuclear workers), and 4) radioactive fallout from nuclear weapons testing.

Health outcomes associated with exposure to ionizing radiation are related to its carcinogenic, genetic, and/or teratogenic effects (i.e., from prenatal exposure). Ionizing radiation is presumably capable of inducing all forms of human cancer, with the exception of Hodgkins lymphoma and chronic lymphocytic leukemia. However, because of the differential radiosensitivity of various body tissues, carcinogenic effects vary by site. The more common radiogenic cancers include leukemia, non-Hodgkin lymphoma, multiple myeloma, lung cancer, thyroid cancer, brain/nervous system tumors, breast cancer, ovarian cancer, liver cancer, malignant melanoma, and bone cancers.

In Utero Exposure to Ionizing Radiation: Teratogenic and Carcinogenic Effects. There is sufficient evidence to indicate that direct exposure of the highly radiosensitive rapidly developing embryo and fetus can result in teratogenic and also carcinogenic (i.e., increased risk of subsequent cancer) effects, especially if exposure occurs at critical stages of development. Animal studies have demonstrated the development of malformations associated with exposure during critical stages of organogenesis with doses as low as 50 mGy. Teratogenic effects may manifest as adverse pregnancy outcomes (stillbirths, spontaneous abortions), congenital anomalies, mental retardation, and molecular changes. Although these effects have not been consistently demonstrated in studies of human populations, studies of children, who were exposed *in utero* to ionizing radiation, of A-bomb survivors have reported an increased frequency of microcephaly, mental retardation, reduced IQ and seizures. No excess fetal and infant mortality and other congenital anomalies were seen. However, limitations of these studies include the

underascertainment of early reproductive wastage, high exposure doses, and the role of maternal radiation sickness on outcome.

Several studies have shown that children who were exposed to diagnostic x-rays while *in utero* increase the risk of childhood cancer. However, studies of children exposed to the A-bomb in Japan have not shown a clear excess risk of leukemia and other cancers. However, the number of cancer cases in this cohort was too small to draw firm conclusions.

Genetic (Heritable) Effects-Preconception Radiation Exposure. Genetic alterations in germ cells following maternal or paternal preconception exposure to ionizing radiation can be transmitted to the off-spring, in whom it may manifest as congenital anomalies or cancer. Animal studies have shown that heritable mutations and chromosomal abnormalities can occur following exposure to preconception radiation to germ cells and that the frequency of these abnormalities increases with dose. However, these effects have not been well established in humans. Studies of children born to A-bomb survivors after May 1946 (i.e., conceived after the bombings) have not shown an excess of heritable effects, as measured by adverse pregnancy outcomes (major congenital anomalies, still births, birthweight, neonatal deaths, cancers, and other changes in chromosomal arrangements (including Down syndrome), and also in disturbances in normal growth and development. A case-control study in the United Kingdom had reported an increased risk of childhood leukemia associated with paternal occupational exposure to ionizing radiation prior to conception. However, this hypothesis has been found to be invalid, largely because it could not be replicated in other populations and was not consistent with current understanding of radiation genetics or of the hereditability of leukemia.

Studies of Population Living Near Nuclear Facilities. Many ecologic studies evaluating health outcomes of populations living near nuclear facilities have been conducted in the United States, United Kingdom, Canada and Europe. These studies sought to document whether populations living near nuclear facilities are at increased risk of adverse health outcomes (mainly cancer mortality and morbidity) due to exposure to low levels of ionizing radiation, and if so, what the magnitude of these risks are. Although some studies indicate an increased rate of disease, no study has convincingly been able to demonstrate a link between the increased risk and radiation exposure. Several possible explanations, including methodologic limitations and other environmental factors, such as viral, social factors and chance clusters have been offered for these findings. In addition, limitations of ecologic studies, lack of adequate exposure information (exposure usually defined as living near vicinity of these facilities) with resultant misclassification of subjects and inability to show a dose response and general disregard for statistical power make the findings of these studies inconclusive.

Studies in the Population Living Near the ORR. To date, there have been five published ecologic studies which have evaluated the health risk (mainly of cancer mortality) of the off-site population living near the vicinity of the ORR. None of these studies with the exception of one

showed an excess of cancer in this population. It is difficult to compare these studies because of differences in time periods and population studied and in analytic strategies used. These studies are limited by the problems inherent in ecologic studies ('ecologic fallacy', migration patterns, temporal ambiguity between exposure and development of disease, completeness of ascertainment of cases, and also by their reliance on mortality data). Thus, because of these limitations, it is not possible to draw any firm conclusions from these studies whether the population living near the vicinity of ORR has significantly higher death rates from cancer than expected in other populations.

9. Mercury

Mercury is a naturally occurring element which exists in inorganic and organic forms. The properties of the different species are different and thus the health risks associated with exposure varies by species. Metallic mercury is liquid at room temperature and volatile (vaporizes easily), whereas the inorganic salts are solid and generally insoluble but organic mercury is solid and soluble in water. Individuals are exposed to metallic mercury primarily through the inhalation route, and to inorganic salts and organic mercury primarily through the oral route. Metallic and organic mercury can cross the blood-brain and placental barriers and accumulate mainly in the central nervous system and the kidneys. Inorganic mercury salts, on the other hand, cannot cross the biological barriers and preferentially accumulate in the kidneys. Levels of mercury in blood, urine, and hair are good biomarkers for exposure to mercury.

In Oak Ridge, over 11,000 metric tons (24.2 million pounds) of mercury were used to enrich lithium in its Li-6 isotope for use in the production of thermonuclear weapons in the Y-12 plant, primarily from 1955-1963. According to the Department of Energy, an estimated 900 to 1200 metric tons were lost to the environment (320-440 metric tons) or unaccounted for (500 to 860 metric tons). Of the mercury lost to the environment, 23 metric tons were believed to have been lost to the air, 190 metric tons were lost in spills, and 100-210 were released to East Poplar Fork Creek behind the Y-12 Plant, and subsequently into the flood plains of the East Poplar Creek and eventually into the Clinch River. The species of mercury present in the soil of the flood plains is not clear, though it is believed that most of it is in the form of insoluble mercuric sulfide.

Adverse Health Effects Associated with Mercury. The primary health concerns of exposure to mercury are adverse effects on childhood development, neurologic impairment, and renal function. At high levels, organic mercury can cause serious adverse reproductive outcomes, including Minamata disease and other developmental defects. At lower levels of exposure, the effects are more subtle. A variety of other possible adverse effects have been raised, including dermal/ocular toxicity, respiratory dysfunction, gastrointestinal toxicity, hematologic abnormalities, hepatotoxicity, immune suppression, and adverse reproductive outcomes. However, the biological bases for these concerns are more speculative.

Adverse Developmental Outcomes. The developing nervous system of the fetus is highly sensitive to the toxic effects of organic mercury, which easily enters the fetal circulation after crossing the placenta. The resultant adverse developmental effects of such exposures have been well documented in humans from epidemics of human poisonings, occurring when fish with high levels of mercury have been eaten (e.g., Minamata epidemic in Japan, 1955) or when grain treated with fungicides containing mercury have been widely consumed (Iraqi epidemic, 1971-72). The symptoms observed in offspring of exposed mothers were primarily neurological in origin and have ranged from delays in motor and verbal development to severe brain damage. Subtle changes, such as small changes in intelligence or learning capacity, have not been extensively evaluated. However, at lower levels of exposure to methyl mercury, the neurodevelopmental effects are less well established, although available evidence indicates that neurobehavioral dysfunction in children may occur if the maternal mercury concentration in hair is >6 μg/g. Two large ongoing, prospective cohort studies of children in communities of fish eaters with low exposures to methyl mercury followed and assessed subjects at regular intervals (at birth, 6, 12, 24, and 36 months, 5 years, respectively) for neurodevelopmental outcomes. Preliminary analyses from these studies indicate that no consistent adverse effects were detected at exposures less than 10 ppm of mercury in maternal hair.

Neurological Effects. The nervous system is the primary target organ for elemental and methyl mercury-induced toxicity. Much of the data on neurological and behavioral disorders in humans are from occupational studies where inhalation of metallic mercury vapor has been the main source of exposures. The neurologic and behavioral manifestations associated with mercury exposure encompass a broad range and are non-specific. Specific symptoms include tremors, emotional lability, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy, and performance deficits in tests of cognitive and motor function. Most of these effects were seen after exposure to high concentrations of mercury vapor, which represents toxicity related to acute tissue exposure to inorganic mercury. However, increased tremors and cognitive difficulties are thought to be sensitive manifestations for chronic low-level exposure to metallic mercury vapor.

Renal Effects. Human data on renal toxicity have been primarily based on case series with high exposures due to ingestion of contaminated foods (meat, fungicide treated wheat seeds) and workers occupationally exposed to elemental mercury. Although adverse renal effects following exposure to metallic, inorganic, and organic forms of mercury have been reported, there is no well defined clinical entity. Early manifestations include proteinuria, and depending on the severity of the renal toxicity, hematuria, oliguria, urinary casts, edema, and inability to concentrate urine and may rarely even lead to the nephrotic syndrome (a clinical condition characterized by proteinuria, hypoalbunemia, hyperlipidemia, oval fat bodies and casts in urine, and edema). The condition may rarely even progress to renal failure. However, except with poisoning cases, in the present era with regulated occupational exposures, manifestations of renal toxicity are rare and, if any, more subtle.

10. Polychlorinated Biphenyls (PCB)

Polychlorinated biphenyls are a family of man-made compounds that are ubiquitous and persistent in the environment. They are synthesized by chlorination of biphenyls leading to the replacement of 1-10 hydrogen atoms by chlorine. The number of chlorine atoms and the position they assume in the biphenyl molecule determine the properties and toxicity of individual congeners, up to 209 of which are known to exist, though only 36 are considered to be environmentally relevant. PCBs exist in an oily form and because of their excellent thermal and chemical stability, have been widely used as dielectric fluids in large, commercial transformers and capacitors and for formulation of lubricating and cutting oils for machining tools. In the US, commercial mixtures are known as Aroclors. Production of PCBs has been banned in the U.S. since the 1970s because of concerns for public health.

Exposure to individuals in the occupational setting is primarily through inhalation, and some through the dermal route. Exposure to the general population is mainly from ingestion of contaminated food (primarily fish, dairy products) and water, and some through the dermal route by coming in contact with PCB contaminated soil and water (usually during recreational activity). PCBs are easily absorbed through the gastrointestinal tract if ingested or through the lungs if inhaled, and are distributed throughout the body, preferentially accumulating in adipose (fatty) tissues because of its lipophilic nature and some in the liver. They are metabolized in the liver and excreted mainly in the feces (if ingested) and in the urine (if inhaled). Because of its high fat content, maternal milk has higher concentrations of PCBs and is an important route of excretion. Thus, maternal milk is an important exposure pathway of PCBs for nursing infants. Being lipophilic, PCBs readily cross the blood-brain and placental barriers. Thus, PCBs from maternal blood can readily enter the fetal circulation and accumulate in the developing fetus. Levels of PCB in serum, milk, and adipose tissues are good biomarkers of exposure.

In Oak Ridge, PCBs were used as machine coolants and cutting oils in the production of enriched uranium weapon parts at the Y-12 Plant, and the enrichment cascade lubricating oil at the K-25 Plant. The millions of gallons of PCBs used over the years were disposed in a variety of ways, including: in storage tanks some of which leaked, plowed in an 'oil land farm' within ORR, and by burning in incinerators. Significant PCB levels have been identified in the aquatic flora from Watts Bar lake up to the Clinch River. In addition to releases from the ORR, other sources of PCB releases have been identified.

Adverse Health Effects Associated with Polychlorinated Biphenyls. For high-dose exposures, primarily occupational or poisoning, there are well-established adverse dermo-ocular effects. However, of greater concern are the effects of chronic exposure to much lower doses. Studies in animal and *in vitro* models have suggested potential effects that may result from chronic, lower dose exposures. Although a variety of adverse effects have been postulated to be related to PCBs, none of these have been well established. PCBs are known to induce hepatic microsomal enzymes and also affect lipid levels, such as serum cholesterol. However, the clinical

significance of these findings is unclear. Those with the greatest degree of plausibility (primarily because of the number of studies with consistent findings) are carcinogenesis and neurodevelopmental effects; however, the evidence is such that this topic remains highly controversial.

Cancer. Animal studies indicates that mixtures of PCBs induce preneoplastic lesions and hepatocellular carcinoma in animals when given in appropriate doses for extended periods of time. Based primarily on the animal data, the EPA has classified PCBs as probable carcinogens. The relatively few studies of cancer in humans have been limited primarily to mortality studies of workers in commercial transformer and capacitor plants exposed occupationally to PCBs. Cancers reported included malignant melanoma, hepatobiliary, brain, and kidney cancers. Although these studies have shown possible association of PCBs with cancer, the findings are inconsistent and inconclusive, mainly because of inadequate measurements of PCB exposures, relatively small sample sizes and relatively short follow-up span for rare malignancies, variable quality of data on causes of death, and inadequate control for other concurrent chemical exposures and confounding factors.

Developmental Effects. The association between pre- and post-natal exposure of PCBs and subsequent development has been studied extensively in two cohorts of children in the U.S.: the Michigan children cohort and the North Carolina children cohort. Baseline and follow-up studies of these two cohorts have reported 1) neurodevelopmental effects manifested as motor deficits at birth, 2) impaired psychomotor index during the first year of life, 3) impaired visual recognition memory at seven months of age, and 4) deficits in short term memory at 4 years of age in those with highest transplacental exposure to PCBs. These deficits were no longer present at ages 3, 4, and 5 years. Review of school performance from report cards in the North Carolina cohort did not show any difference between transplacental PCBs or exposure to PCBs through breast milk. However, the limitations of these studies, including questionable PCB exposure assessment, selection and comparability of exposed and control subjects, have raised concerns, making the results of these studies inconclusive. Nevertheless, it is noteworthy that some of the neurobehavioral deficits were observed at levels of PCBs commonly found in the general population in the US.

11. Recommendations

As the main dose reconstruction study progresses, the extent and magnitude of releases and possible human exposure from the current four priority contaminants may be confirmed. Identification of the exposed populations and quantitative estimates of their exposure levels obtained from this process will greatly facilitate in evaluating the feasibility, planning and conduct of any future epidemiologic study. The following discussion is based on our review and understanding of the potential health impact from off-site releases of contaminants from the ORR, identified in Phase I of the Dose Reconstruction Study, to the population living near its vicinity.

Perspective. There is a variety of rationales for conducting epidemiologic studies of the health effects of environmental contaminants. In this discussion, our perspective is that of public health. From this perspective, the motivation for conducting an epidemiologic study is to obtain scientifically valid, quantitative estimates of the adverse health effects of exposures with the goals of:

1. Advancing understanding of the disease causation process, so as to further public health initiatives to reduce risk in the future;

2. Determining and documenting the effects of current and on-going exposure, if any, to facilitate steps to decrease health hazards immediately.

Clearly, there are other motivations for epidemiologic studies. For example, given past exposure of a population to a contaminant with known risk, it might be desirable to quantify health effects for medicolegal purposes. Although such a perspective is not taken here, the approach taken is nevertheless applicable.

Criteria for Initiating Epidemiologic Studies. Because of the difficulty and expense of conducting scientifically valid epidemiologic studies with a public health perspective, such studies should only be initiated after careful consideration of the rationale and possible return. Each specific contaminant-health outcome pair must be carefully assessed. Although determining whether to initiate a study always requires a large component of judgement, there are several broad criteria that can be applied. These are outlined below.

1. **Material potential exposure of the population to the contaminant.** If only a small number of persons were potentially exposed or the levels of exposure were sufficiently low, then the question is of more limited public health relevance;

2. **Reasonable scientific basis for concern.** The rationale for concern might consist of:

   a. Biological effects of the contaminant, such as chromosomal damage;
   b. Animal studies, such as increased tumerogenicity;
   c. Human studies, including suggestive epidemiologic studies, case series, etc.

3. **Material scientific uncertainty regarding actual health effects.** Given a basis for concern, there needs to be uncertainty regarding the actual health effects. If there is reasonable certainty that the exposure is harmful, then public health activity should be directed at reducing exposure rather than further study. However, this criterion may not apply in some situations. For example, if the purpose of a study were to determine and document what happened to persons (in

terms of health effects) exposed to a contaminant in the past, one may initiate the study regardless of the scientific certainty that exposure to the contaminant causes disease. Similarly, there could be reasonable certainty that an exposure (in general terms) is harmful, but more subtle effects - which could be important in practical terms - could well require further study. Although this criteria should be considered, clearly it is of lesser significance than criteria #1 and #2 above.

4. **Feasibility and cost of study.** Even studies that meet 1-3 above may not be feasible, for example, because of inadequate sample size and availability of data sources. Studies that are in theory feasible may have excessive costs that may not be justifiable given the health effect of concern and/or limited available resources.

Iodine-131. For this contaminant, there was clearly wide population exposure at some level, a reasonable basis for concern of increased risk of thyroid disease above certain exposure levels, and yet, a reasonable scientific uncertainty about the association between iodine-131 and thyroid disease. Thus, although this contaminant meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, as discussed below. .

Based on Phase I results of the Dose Reconstruction Study, an estimated 300,000 Ci of ^{131}I (estimated releases from the Hanford Reservation were 740,000 Ci of ^{131}I) was released from the RaLa operations in the X-10 facility from 1944 to 1956. However, the amount of ^{131}I releases may be significantly lower, based on more recent Phase II data. Because of a very short radioactive half-life of 8 days, ^{131}I did not persist in the environment and so is not a current exposure hazard. However, based on the initial magnitude of ^{131}I releases, it is possible that some historically exposed individuals may have developed thyroid disease.

Dr. Scott Davis is currently conducting a CDC-funded, retrospective cohort study of ^{131}Iexposure and thyroid disease in Hanford, Washington State, called the Hanford Thyroid Disease Project. This is a state of the art study using dosimetry data to estimate individual radiation doses to study dose-response effects. The study has set up a comprehensive logistical framework to trace and locate individuals, identified from birth certificates, born nearly 50 years earlier and and to interview them (and their parents) in great detail and to conduct a comprehensive clinical examination of the thyroid gland. The final results of the Hanford Thyroid Disease Study are expected to be released in mid-1998. We thus recommend that the Panel not consider such a study in Oak Ridge, at present. A similar study in Oak Ridge would be very expensive (cost of the Hanford Study is an estimated $16 million), and unlikely to provide new scientific insight. However, the latter point may be less relevant if the main purpose of an epidemiologic study at Oak Ridge were simply to demonstrate whether people who were significantly exposed developed any adverse health effects. As an alternative to a full-fledged epidemiologic study, the Hanford dose-response results could be used to characterize risk to the Oak Ridge exposed population.

Cesium-137 and Other Radionuclides. Although results of the dose-reconstruction study are needed, it seems that the potential for wide exposure to low levels of ionizing radiation from these radionuclides is present. Furthermore, there is a basis for concern for several radiation-linked cancers, primarily acute leukemias, and neurodevelopmental (microcephaly, mental retardation, such as lower IQ) and birth defects. Despite this basis for concern, there is no scientific certainty that the low level doses probably characteristic of the exposures in the Oak Ridge catchment actually increase risk of these diseases. Thus, although this group of contaminants meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, which is considered for a retrospective cohort study. Retrospective cohort studies are attractive because they are the most economical among cohort designs. However, the primary difficulty is in defining study groups (i.e., the cohort) without estimates of exposure that occurred in the remote past and for which there are no individual records of exposure. The findings of the dose reconstruction study and the attendant uncertainty analysis should allow for defining groups of people who were exposed, exposed at various levels, or unexposed. Thus, pending further information from the dose reconstruction study, retrospective cohort studies do not appear feasible because of the absence of valid past exposure data.

Mercury. Outcomes of concern for mercury are childhood intellectual and motor development, neurologic toxicity, and renal toxicity. There is possible wide distribution of the contaminant, a scientific basis for concern, yet genuine scientific uncertainty at lower levels of exposure. Thus, although mercury meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, which is considered for a retrospective study. As discussed for radionuclides, retrospective cohort studies may not be feasible, primarily because of the difficulty in defining population groups who were exposed in the past and the lack of well-defined health effects associated with low levels of exposure. To the best of our knowledge, there are no reliable biomarkers of historical mercury exposures. We also are unaware of any systematic set of stored biological specimens (bloods, tissues etc) that could be used for exposure definition. The findings of the dose reconstruction study and the attendant uncertainty analysis should allow for defining groups of people who were exposed, exposed at various levels, or unexposed. Thus, pending further information from the dose reconstruction study, retrospective cohort studies do not appear feasible. Furthermore, health effects related to low level, chronic exposures to mercury do not present as well defined 'clinical syndromes' that can be easily ascertained retrospectively. For example, it would be infeasible to retrospectively ascertain intention tremors or memory loss, established effects of mercury exposure, from medical records. Even with information from the dose reconstruction study, a retrospective study would pose enormous problems.

Polychlorinated Biphenyls. Similar considerations are present for PCBs. Outcomes of concern for PCBs include childhood intellectual and motor development, and cancer (although which specific type is not clear). There is possible wide distribution of the contaminant, a

scientific basis for concern, yet genuine scientific uncertainty at lower levels of exposure. Thus, although PCBs meet criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues again are feasibility and cost, which is considered for a retrospective study. As discussed for radionuclides, retrospective cohort studies may not be feasible, primarily because of the difficulty in defining population groups with exposure in the remote past. Although the half-lives of some higher chlorinated PCBs have been reported to be as long as 17 years in fatty tissues, we are not aware of reliable biomarkers of practical use to measure historical PCB exposures. We also are unaware of any systematic set of stored biological specimens (bloods, tissues etc) that could be used for exposure definition. Thus, pending additional findings of the dose reconstruction study, retrospective cohort studies do not appear feasible because of the absence of valid past exposure data.

Recommendation: Bioprevalence Study. Based on Phase I results of the Dose Reconstruction Feasibility Study, three of the priority contaminants (mercury, polychlorinated biphenyls, and radionuclides such as ^{137}Cs) are still persistent in the environment, primarily in aquatic biota and sediment beds of the Clinch River and the Watts Bar Reservoir. The main sources of releases were from the Y-12 facility into East Fork Poplar Creek and its flood plains for mercury, from the X-10 facility to White Oak Creek for ^{137}Cs and the other radionuclides, and from the K-25 plant to the Clinch River and at least three other upstream sources for PCBs. Ultimately, all three contaminants drain into the Clinch River which in turn drains into the Tennessee River before Watts Bar Dam. The long half-life of ^{137}Cs (30 years) and the persistence of both mercury and PCBs mean that they continue to persist in the environment and continue to be of potential risk for humans.

However, for each of the contaminants considered, a crucial question is the level of current exposure in the population. If a large number of persons have high exposure levels then epidemiologic studies are warranted, though they may not always be feasible. Although the dose reconstruction studies and uncertainty analysis are the only practical way to obtain information on past exposures, current exposure can be assessed with bioassay, particularly for mercury and PCBs. The samples obtained for such assays can be preserved, which would permit future studies as assay techniques improve or if there are new contaminants of concern.

Thus, a bioprevalence study should be considered. The study could focus on one or more defined population groups. Studies of infant-mother pairs while in hospital and adults could be investigated. Infant-mother pairs could be identified from the birthing facilities most likely to be used by the population at risk (e.g., Methodist Medical Center of Oak Ridge) over a defined period of time. For adults, a random sample of the population could be surveyed. Sampling could be stratified by areas believed to be more contaminated to insure selection of individuals at higher risk for exposure.

The surveys should encompass both the Oak Ridge area and another region in Tennessee,

as a control group, to be surveyed concurrently. A control group in another Tennessee population, matched on several population characteristics (e.g., proportion of population that are white, black, urban, rural, high school graduates; mean family income, population, mortality and infant mortality rates) is desirable to address the issue of whether the population of the Oak Ridge area is at higher risk from exposure to these contaminants than a comparable population. Although comparison with existing population reference standards alone is an alternate option, this has the potential for biases introduced by incomparability of populations, time trends in environmental levels of contaminants and measurement techniques. Thus, a separate comparable control population should be surveyed concurrently to minimize such biases. On the other hand, if the study objective were to simply evaluate the levels of exposure to a contaminant at which adverse health effects can be demonstrated in the Oak Ridge population, subjects with no/minimal exposures would serve as the reference group and an independent comparison group would not be necessary. However, our understanding is that this is not the main objective.

Samples of hair, urine, and blood could be obtained and multiple contaminants (PCBs, mercury) assessed. In addition, data can be collected on demographic characteristics, health status, dietary (such as, fish consumption for mercury and PCBs) and other potential sources (such as, recreational activities, occupation, and use of dental amalgam for mercury) of exposures from survey questionnaires of subjects.

The major advantages of this approach are that 1) it is a first step in addressing current public health concerns in a scientifically valid method, 2) levels of current contaminants can be directly measured in individuals which can help prioritize contaminants of greater concern, 3) multiple contaminants can be measured, 4) specimens can be stored, so that prevalence levels of contaminants of concern identified in the future can be measured and/or as better assay techniques are developed, the current contaminants can be reassessed, 5) it can provide needed information on exposure levels and dose variances to calculate sample size and power for future studies, and 6) it can be used to validate the models used for exposure or body burden assessment or to check the accuracy of predictions made by such models. Given the length of time and large amount of resources required to conduct a meaningful epidemiologic study, a bioprevalence study would be an important starting phase, before other studies are considered.

Contingent on the findings of such a survey and availability of funding, for example, a prospective long-term, cohort study of newborn infants for birth defects and neurodevelopmental outcomes could be considered. Exposures from the contaminants (radionuclides, organic mercury, and PCBs) discussed above appear to share similar pathways with considerable overlap of the resultant exposed population. There is concern that prenatal exposure to these contaminants may adversely affect the fetus which may manifest in neurodevelopmental effects in infancy and childhood. Thus, such a study has the potential advantage of being able to evaluate the association between exposure to multiple contaminants and risk of a common health effect (neurodevelopmental) in a susceptible population, such as newborns. Furthermore, unlike adults,

there is no temporal ambiguity between exposure and development of adverse health effects. The initial bioprevalence survey would provide precise, current exposure levels of contaminants in the population, and assist in determining sample size requirements for these type of studies.

Investigation of Reported Clusters. The main thrust of the Oak Ridge Health Studies has been contaminant driven. That is, a specific contaminant with significant off-site releases to which the population may be exposed is first identified. The risk of adverse health effects associated with exposure to such a contaminant is then assesed. However, there may be reports from the public of possible clusters of some diseases or illness, independent of this process, that the State Health Department may need to respond to. A good example is the current investigation of a possible cluster of amyotrophic lateral sclerosis (ALS) in the Oak Ridge area, which was reported by members of the public. In order to systematically be able to respond to such reports, we recommend that an excellent monograph entitled "Guidelines for Investigating Clusters of Health Events" published by the Centers for Disease Control in its *Morbidity and Mortality Weekly Review Supplement* in August 1990 be used as a framework for developing a tailored protocol. The dose reconstruction and bioprevalence studies will help further define the probability that future cluster outbreaks are linked to contaminants.

ATTACHMENT 1
ORHASP-Feasibility of Epidemiologic Studies in Oak Ridge
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ORHASP: FEASIBILITY OF EPIDEMIOLOGIC STUDIES

FINAL REPORT

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1. Background/History

In September 1942, the U.S. Federal Government established the Oak Ridge Reservation (ORR) in a remote farming community in eastern Tennessee for the production of fissionable materials for building nuclear weapons as part of the Manhattan Project. The ORR included three main facilities: the Oak Ridge Gaseous Diffusion Plant (code named K-25) for production of enriched ('bomb grade') uranium through a gaseous diffusion process; the Y-12 facility for production of enriched uranium through an electromagnetic separation process; and the X-10 facility (now called the Oak Ridge National Laboratory [ORNL]) with a graphite reactor for producing plutonium and a chemical separations plant. The ORR produced enriched uranium for the world's first atomic bomb, which was dropped over Hiroshima, Japan on August 6, 1945[1].

After the War, the ORR continued to play a major role in the U.S. nuclear weapons program, but in addition significantly expanded its mission to include basic and applied research for peacetime use of nuclear energy. The K-25 facility continued to produce enriched uranium for use as fuel for nuclear reactors until 1985. This facility now houses hazardous wastes (low level radioactive as well as chemical wastes) from the other ORR operations and other out-of-state Department of Energy (DOE) sites. The Y-12 facility's main mission has been to fabricate nuclear components, process source and special nuclear materials, and to provide support for other weapons-design laboratories. An important post-war mission of ORNL has been to conduct research and development of peacetime applications for nuclear energy; such as production of radioisotopes for diagnostic and therapeutic use in medicine and also for some industrial applications[1].

The city of Oak Ridge and the DOE ORR are located 40 km to the west of Knoxville, Tennessee (Figure 1-1). The ORR is located within the corporate city limits of the City of Oak Ridge, in Roane and Anderson counties, in eastern Tennessee. It consists of approximately 35,236 acres of federally owned lands, and is bounded on the north and east by the populated portion of the City of Oak Ridge and on the south and west by the Clinch River (Figure 1-2). Except for the City of Oak Ridge (population 28,000), the land within 8 km of the ORR is predominantly rural, and is used largely for residences, small farms, and pasture land[1].

The approximate location and population (1980 census data) of other towns near the ORR are Oliver Springs (population 3600), 11 km to the northwest; Clinton (population 5300), 16 km to the northeast; Lenoir City (population 5400), 11 km to the southeast; Kingston (population 4400), 11 km to the southwest; and Harriman (population 5400), 13 km to the west. Figure 1-3 shows the locations of these towns in relation to the ORR. Knoxville is the nearest major metropolitan center, and has a population of about 183,000[1].

During the past fifty years, enormous quantities of radioactive and hazardous chemicals have been utilized in the operation of these three facilities. Production, research, and waste disposal operations at all three of these facilities have resulted in inadvertent releases of hazardous and radioactive wastes to the environment (outside the ORR). These releases have impacted the environment by contaminating the surrounding air, soils, sediments, vegetation,

animals, ground water, and surface water. Depending on their physical and chemical properties and the size of the continuing dose through completed pathways, some of the materials have persisted longer than others in the environment. The human population living in the area may thus have been or continue to be exposed through these pathways with increased risks to their health.

Because of potential health hazards of working in these facilities, workers were and continue to be monitored carefully. Several mortality and morbidity studies of worker cohorts looking at adverse health effects associated with exposure to radiation or to hazardous chemicals in these DOE managed facilities have been published[2-5]. However, meaningful studies of potential adverse health effects to the population living near the vicinity of such facilities have been largely non-existent and limited mainly to ecologic correlations of cancer mortality data. It may not be appropriate to extrapolate studies of health effects in workers to the general population. This is primarily because workers represent a highly selective, predominantly healthy population ('healthy worker') and also the nature of their exposure ('occupational') may vary considerably in intensity, form, route, and duration from that of the general population.

The Tennessee Department of Health (TDH) and the United States Department of Energy (DOE) signed an agreement in 1990, called the Oak Ridge Health Studies Agreement. In this agreement, the DOE would provide funding to the State for coordinating independent health-related studies to evaluate the potential health risks to off-site populations possibly exposed to hazardous materials from past and present ORR operations. An independent Steering Panel (ORHASP) was set up to advise and provide direction to the study.

Phase I of the study, which was completed in September 1993, was called the Dose Reconstruction Feasibility Study. Its primary goal was to determine the quality, quantity, and potential usefulness of the available data for reconstructing historic releases and subsequent exposure pathways of chemicals and radionuclides. The plan was to evaluate feasibility of further dose reconstruction studies and also where feasibility was established, to perform preliminary screening analyses to identify priority contaminants for focused efforts in future larger studies. Chemrisk, the Phase I contractor, identified the following contaminants that appeared to have the greatest potential for causing adverse health effects and were thus targeted for full dose reconstruction studies. These contaminants (Table 1-1) are: radioactive iodine (^{131}I), radiocesium (^{137}Cs) and other radionuclides, mercury, and polychlorinated biphenyls (PCBs). During the main dose reconstruction study, other contaminants will also be screened.

ORHASP recognized there may be a need to supplement findings of the main dose reconstruction studies, that are limited to estimates of health risk in a given population, with possible epidemiologic studies in future to directly evaluate health outcomes. ORHASP commissioned investigators from the Department of Preventive Medicine at Vanderbilt University to explore the feasibility of initiating meaningful, valid epidemiologic studies to address potential health concerns in the off-site population of Oak Ridge and its surrounding areas.

The scope of work included the following (see Appendix A):

A. Develop guidelines for determining the need for an epidemiologic study.

B. Tasks relating to the feasibility study

- Review contaminants of concern selected by ORHASP
- Review/select possible health outcomes and review relevant epidemiologic literature
- Review data needs/sources/availability
- Provide general epidemiologic support to the ORHASP
- Meet with selected groups and individuals in the community, as needed
- Prepare and submit final report

This report has been prepared in fulfillment of the above contract. The report is divided into eleven sections. Sections one and two describe briefly the background and rationale for epidemiologic studies in the population living in the vicinity of the Oak Ridge Reservation, respectively. Section 3 presents an overview of common epidemiologic designs and sections four and five describe the elements needed for conducting valid cohort and case control studies, respectively. Section six lists an inventory of potential data sources that are available for conducting epidemiologic studies in Tennessee and Oak Ridge. Sections seven through ten briefly characterize the four priority contaminants released from ORR operations and the health effects possibly associated with these contaminants. Section eleven describes our recommendations.

Table 1-1 Priority Contaminants Identified from Phase I Dose Reconstruction Studies for Further Study (Source: Oak Ridge Health Studies: Phase I Report, September 1993)

Contaminants	Facility	Years of Highest Releases	Process
Iodine-131	X-10 (ORNL)	1944-1956	Radioactive Lanthanum (RaLa) Processing
Cesium-137 and Other Radionuclides	X-10 (ORNL)	Late 1943-1960s	Various Chemical Separation Programs
Mercury	Y-12	1955-1963	Lithium Separation and Enrichment Operation
Polychlorinated Biphenyls	K-25/Y-12	Indeterminate	Transformers/Machining

2. Rationale for Health Effects Study

There are several reasons why a health effects study could be undertaken. First, in an open, democratic society, citizens have a right to know whether some activities undertaken by their government, whether in the past or the present, have in any way increased the risk to their health or adversely affected it. Knowledge gives members of a community the means to deal with such true or perceived health risks, regardless of when the exposure may have occurred. Second, it is important to know whether there are current hazards that might adversely affect public health. If there are, appropriate actions can be taken to minimize health risk to the public. Third, a health effects study may identify evolving health problems associated with exposure to hazardous materials in the past. In such instances, exposed individuals could be screened for early detection and treatment of disease, and also for medical follow-up, if needed. Finally, a health effects study could be done primarily for advancing scientific knowledge and understanding of whether a contaminant has any adverse health effects.

If doses are well enough known, it is necessary to prioritize what contaminant(s) to study, given the large number of radionuclides, metals and chemicals used in the past and in the present at the ORR,. For example, resources could be allocated to evaluate health effects associated with some exposure in the distant past that no longer exists and thus no remedial action can be taken. On the other hand, they could be allocated to evaluate health effects associated with exposures that may still exist and thus be suitable for remedial action. The answers to these questions are policy choices, based on existing scientific knowledge and on the level of public concern, among others. This report does not describe the general epidemiologic support we provided to ORHASP and the meetings we had with individuals in the community.

3. Epidemiologic Study Designs

Epidemiology is the study of the distribution and determinants of diseases and injuries in the human population. It can be broadly categorized into descriptive and analytic epidemiology. Generally, descriptive studies (case series, cross-sectional, ecologic studies) are used to describe frequency and patterns of disease with regard to person, place, and time, and provide broad comparison of rates of disease. These types of studies can be done relatively quickly and at low cost. However, because of inherent limitations of these study designs discussed below, descriptive studies are generally useful for generating hypothesis (i.e., providing direction for future research) and not for establishing causal inferences. Analytic studies (experimental, cohort and case control studies), on the other hand, are used for studying the etiology (risk factors) of disease to provide evidence for establishing causal inference. We will discuss some of the basic elements of these designs in the following sections, starting with the analytic studies. Refer to the glossary in the back of the report for common epidemiologic terms.

3.1 Epidemiologic Study Design Options.

Epidemiologic study designs available for population-based research include experimental studies and a variety of observational designs (Figure 3-1). In experimental studies, the investigator manipulates the factor (i.e., exposure) of interest. For example, in clinical studies of therapeutic drug effects, subjects are **randomly** assigned into experimental and control groups. Randomization produces groups that are comparable to each other not only with respect to known factors but also unknown factors (free from confounding and selection bias). Thus, if properly conducted, any differences in outcomes between the treatment conditions reflects differences between the treatments per se. Methodologically, this is the 'gold standard' study design for testing etiologic hypotheses. Unfortunately, this is not a viable design option in environmental epidemiology because

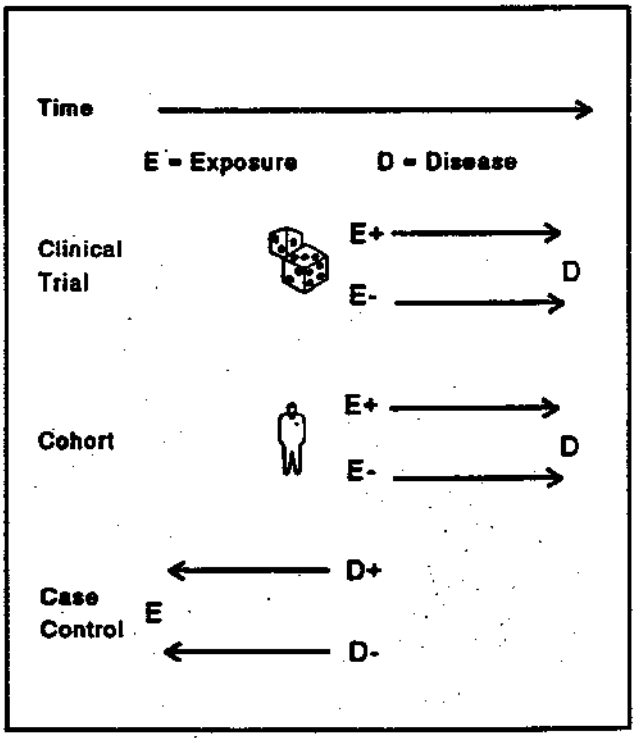

Figure 3-1 Primary study designs.

The material in this section has been adapted from "Pharmacoepidemiology Notes" by Wayne A. Ray, Ph.D., Department of Preventive Medicine, Vanderbilt University School of Medicine

it is impossible, unethical, or infeasible to manipulate the exposure of interest. Issues pertaining to environmental exposures must be studied with observational designs. Unlike experimental studies, the investigator has no control over who gets exposed in observational studies. Thus, the overriding concern for these designs is controlling for the effects of factors (confounding variables) other than the exposures of interest.

3.2 Cohort Studies.

The structure of a cohort study resembles that of a clinical trial. Groups of subjects with and without the exposure of interest (E) are identified. For studies of chronic disease, the cohort usually is free at baseline of the disease (D) under study. The groups are then followed over time to ascertain outcomes (end point) and rates between the two groups are compared. Some cohort studies, particularly in occupational health, explicitly identify only the exposed group and compare rates of disease to those from a standard reference population (the external controls; e.g. cancer mortality rates in the U.S. population). This strategy has two problems. First, the reference population may be quite different from the cohort (e.g., the "healthy worker" effect). Second, if the exposure is not uncommon, the reference population is not an exposure free group. Depending on the timing of disease (outcome) occurrence, cohort studies are classified as **prospective** or **retrospective (or historical)**. In a prospective study, the cohort is assembled at the beginning of the study and then followed into the future for any occurrence of disease. A retrospective cohort study is different from the prospective cohort design in that the disease (end point) being studied has already occurred and the follow-up period is complete when the study begins. The cohort of disease-free individuals with (and without) the study exposure is identified historically, usually with the help of existing records. A major advantage of this design is that while it retains the major strengths of the prospective design, it can be done quickly with less resources. However, a serious limitation of the retrospective design is its reliance on the availability of reliable and valid records in defining exposure, measurement of confounder and ascertainment of disease occurring in the past. Nevertheless, it is widely used in epidemiologic studies of occupational exposures. Table 3-1 lists the strengths and limitations of cohort studies.

One of the first studies of the adverse effects of smoking was a cohort study of British physicians conducted by Sir Richard Doll[6]. British physicians were mailed a questionnaire that sought information on smoking habits. Death certificates were used to identify fatal lung cancer; analysis demonstrated a 10-fold increase in mortality rates among heavy smokers. In the field of radiation epidemiology, cohort studies of the atomic bomb survivors have provided a wealth of knowledge regarding the adverse health outcomes associated with exposure to ionizing radiation. An illustration of a retrospective study is presented below.

Table 3-1 Strengths and Limitations of Cohort Studies

Strengths	Limitations
If prospective, minimizes bias in the ascertainment of exposure	Is inefficient for the evaluation of rare disease, unless the rate in exposed persons is high
Allows direct measurement of incidence of disease in the exposed and non-exposed groups	If prospective, can be extremely expensive and time consuming
Is of particular value when the exposure is rare	If retrospective, requires the availability of adequate records
Can examine multiple effects of a single exposure	Need to identify and classify people based on exposure. Can be difficult to track changing exposure over time
	Validity of the results can be seriously affected by losses to follow-up

Tumors following radiotherapy in childhood

The study of Ron and colleagues[7], which studies the association between radiotherapy for tinea capitis (ringworm) and nervous system tumors illustrates the retrospective (also called *historical*) cohort study design.

Medical records were used to identify 10,384 Israeli children (the E^+ group) who had received such treatment between 1948 and 1960. The unexposed group (E^-) consisted of 10,384 non-irradiated, unrelated children identified from the Central Population Registry, and 5,392 non-irradiated siblings.

For each child, dose of radiation to the brain was estimated from information in the records on therapeutic dose, treatment techniques, number of courses of therapy, and simulation studies performed using a simulated model of a 6 year old child. Records also provided information on demographic characteristics.

For each child, follow up began on the date of the first treatment and extended through 1982, the date of death, or the date of first tumor. The average follow-up was 26.4 years per child. During the follow up period, tumors of the brain or nervous system were ascertained from the Israel Cancer Registry, hospital pathology records, and death certificates. Tumors included both malignant and benign gliomas, meningiomas, nerve-sheath tumors, and others. All occurrences were validated when possible by review of pathology reports. A total of 73 tumors were so identified.

The investigators found a striking association between estimated doses to the brain and tumor incidence (Figure 3-2).

This study illustrates the advantages of retrospective cohort studies. First, the cases of study disease had already occurred at the time the study began. Because existing records were

used to identify and follow up the cohort, the investigators did not need to wait 26 years to observe the development of tumors. Second, use of records is more economical and less intrusive than direct subject contact. Third, this type of "natural experiment" provides valuable data unlikely to be available prospectively. Despite these advantages, retrospective studies are feasible only if there are available data sources which can be used to accurately define the exposures, determine major confounders, and reliably ascertain disease occurrence.

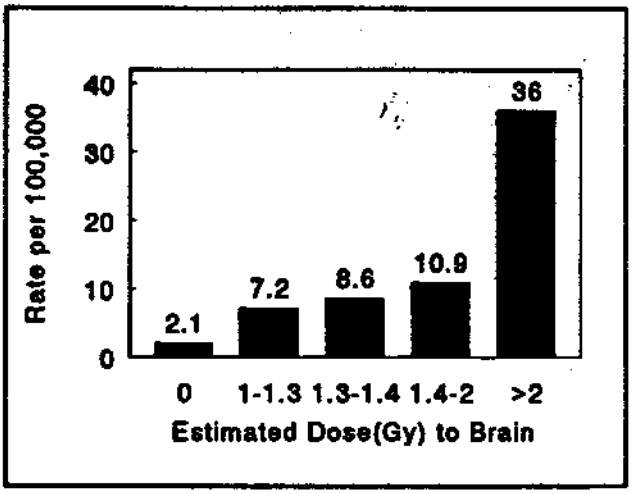

Figure 3-2 Incidence of brain tumors by estimated dose to brain.

3.3 Case-Control Studies.

The case-control study identifies groups of subjects with and without the disease (D) of interest and determines the exposure (E) prior to disease onset in cases and for a comparable time in controls. The frequency of exposure in cases is compared to the frequency in controls. For example, when an excess number of childhood leukemia cases were reported in a population living near the Sellafield nuclear plant in West Cumbria, Great Britain, Gardner and colleagues conducted a case-control study[8]. They identified all cases of leukemia occurring in the West Cumbria Health Authority between 1950 and 1985 and selected controls matched to cases by birth, gender, mother's residence in the area. Data were collected from multiple sources, including medical records, maternal and paternal questionnaires, and Sellafield employment records. They found that paternal employment at Sellafield was associated with risk of leukemia in children, even after controlling for other risk factors. Table 3-2 lists the strengths and limitations of case control studies.

An increasingly popular variant of a case-control study is called a **nested case control study**. This is really a case control study within a retrospective or prospective cohort study. In a nested case control study, members of a specified cohort who develop the disease (cases) of interest after a specified follow-up period are first identified. A sample of cohort members who have not developed the disease (controls) is then selected. The frequency of exposure in cases is compared to the frequency in controls, similar to a case control study. A major advantage of this design is that while retaining the strengths of a cohort study, it significantly reduces the size and cost of the study and increases its efficiency. However, a major disadvantage of this design is that disease rates (and thus estimates of relative risk) cannot be calculated directly, unlike a cohort study.

For example, Wolff and colleagues[9] conducted a nested case-control study of blood levels of organochlorines and breast cancer in a cohort of 14,290 women who had been enrolled in the

New York University's Health Study between 1985 and 1991. At baseline, these women had undergone mammography screening and also provided blood samples which were frozen and stored. Fifty women who subsequently developed breast cancer were included as cases and 171 women who did not develop breast cancer were selected as matched controls from the same cohort. Their exposure to the organochlorines were measured from the original blood specimens. The proportion with significant serum levels of organochlorines among the cases was compared to the proportion with similar levels among the controls, as in a case control study. The authors found that in this population, breast cancer was strongly associated with sera DDE (a metabolite of the pesticide DDT) levels, but not PCBs. In a regular cohort study, one would have had to measure blood specimens for all 14, 290 women, a very expensive proposition.

Table 3-2 Strengths and Limitations of Case Control Studies

Strengths	Limitations
Is relatively quick and inexpensive compared with other analytic designs	Need to identify all cases in a defined population in a defined time, or a representative sample. Otherwise, prone to selection bias.
Is well-suited to study diseases with long latent periods	Cannot directly compute incidence rates of disease in exposed and non-exposed individuals, unless study is population based
Is optimal for the evaluation of rare diseases	Is inefficient for the evaluation of rare exposures, unless the disease rate is very high in exposed persons. Difficult to study specific environmental factors or exposures, especially if the exposures occurred in the distant past. Relying on subject's memory for information increases likelihood of recall bias.
Can examine multiple etiologic factors for a single disease	In some situations, the temporal relationship between exposure and disease may be difficult to establish

3.4 Case Series Studies.

The case-series study is a case control study without the controls. It is particularly useful for identifying potential problems meriting further investigation. However, without a control group, it is difficult to determine whether or not exposure frequency in the cases is different from that expected by chance, unless the outcome is distinctive and is closely linked temporally with the exposure of interest (e.g., use of thalidomide by pregnant mothers and infants with deformed limbs).

3.5 Cross-Sectional Studies.

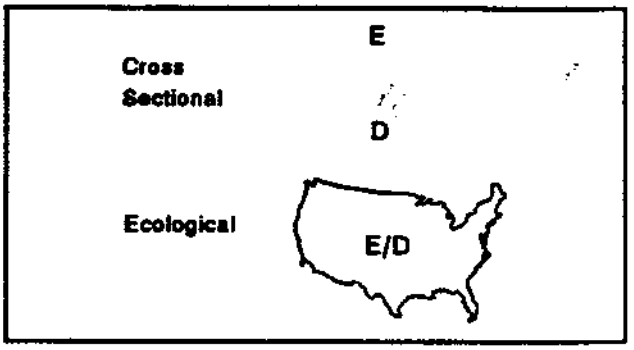

Figure 3-3 Other study designs.

Cross-sectional studies (Figure 3-3) ascertain exposure and disease status at a single point in time. For example, researchers conducted urine screens for benzodiazepines, barbiturates and opiates in 127 Alabama drivers≥55 years of age. Of the 13 with positive urine screens, 77% had at-fault crash involvement in the past 5 years versus 50% of other drivers, suggesting that central nervous system-active drugs increase risk of crash involvement.

Such cross-sectional studies are particularly easy to conduct because all variables are ascertained at a single time, the present. Such studies also have an intuitive appeal because they address the question: "how do people with disease differ from those without disease". However, there are two major problems with cross-sectional designs. First, the temporal sequence is unknown, thus, exposure may follow rather than precede disease. For example, drivers may start anxiolytics, hypnotics, or analgesics following a crash to relieve psychological or somatic symptoms. Second, because the disease cases are prevalent (i.e. new and old cases), the association with exposure is influenced by survival. For example, a survey from Evans County, Georgia found that blacks had a lower prevalence of heart disease than whites. However, this does not necessarily imply blacks have lower risk of heart disease, it also could reflect reduced likelihood of survival.

3.6 Ecological Studies (Correlational Studies).

In ecological studies, the **unit of analysis is a population**. Thus, both exposure and disease rates are determined for large groups of subjects. Very commonly these studies involve comparisons between geographically distinct populations (for example, the studies of correlation between food consumption in different countries and mortality from coronary artery disease), or comparisons of cancer mortality between different geographic areas. Studies of cancer mortality in populations living near nuclear facilities have generally been ecologic ones. Cancer mortality rates in these areas are compared to rates in other geographic areas without nuclear facilities or with the national U.S. rates. These studies are relatively easy to conduct because of availability of data. There are 3 major problems with ecological studies for diseases with multiple risk factors. First is the "ecological fallacy" (defined as inappropriate conclusions regarding relationships at the individual level based on ecological data); those who died of cancer in areas near the vicinity of nuclear facilities may have moved into the area recently and thus would not have had adequate time to have been 'exposed' and develop cancer. Second, is the cross-sectional nature of the analysis; one does not know whether 'exposure' precedes or follows the development of cancer.

Finally, it is difficult to control for other potential causes of cancer.

3.7 Preferred Design.

In addition to the relative merits of individual study designs, there are several important factors which influence the choice of study design. First, the primary purpose of the study must be stated in precise and realistic terms. For example, in a study of health effects of exposure to ionizing radiation, the endpoint(s) to be studied should be clearly specified. The endpoints studied could be cancer (all or specific types?), genetic and/or hereditary effects (which specific effects?). Second, the measurement options available to address the study hypothesis and availability of data must be carefully considered. Are adequate available? Could needed data be collected?. Finally, the resources (time, personnel, and funding) and operations needed to conduct a study must be evaluated. Is it logistically feasible? How long will it take and how much will it cost? Statistical power considerations (described below) then should be used to compare the potential consequences of such alternatives and to guide the selection of the most feasible and cost-effective choice in a particular setting.

In the Oak Ridge setting, the period of highest releases of contaminants appears to have occurred over three decades ago. Thus, a sufficient time interval has elapsed for possible manifestation of endpoints, including diseases with long latent periods, such as cancer. If a cohort of individuals from this time period whose exposure status can be measured is specified and followed-up to the present to ascertain the presence of endpoints, a retrospective cohort study could be done. Thus, for studies of health effects associated with past exposures, a retrospective cohort study would be the design of choice. On the other hand, for studies of future effects associated with current levels of exposure (likely to be much lower than past levels in the Oak Ridge setting), either a prospective cohort or a nested case control study would be designs of choice.

However, the choice of the above designs does not preclude the use of other study designs. As long as one understands the strengths and limitations of the design, there may be situations where a cross-sectional or case series design may be quite appropriate. In the following two sections, (sections 4 & 5) we will briefly discuss the requirements for a valid retrospective cohort study and a nested case-control study, respectively, each illustrated with an example.

3.8 Sample Size and Power of an Epidemiologic Study.

Prior to conducting an epidemiologic study, it is critical to determine the number of subjects needed to answer the question (or questions) posed. Before initiating a study, the required sample size (see sections 4.5 and 5.6 for examples) is calculated by specifying the following:

1. The size of the association (i.e., critical effect) one is interested in detecting (e.g., a relative risk/odds ratio of, for instance, 2 in a cohort or case-control study). The

higher the value of the risk to be detected, the smaller is the sample size required. The smaller the size of the risk to be detected, the larger the necessary sample size.

2. The frequency (or prevalence) of the exposure (i.e., risk factor under study) in the control group (or the general population) in a case-control study and the frequency of the outcome (disease under study, background rate) in the unexposed group (or the general population) in a cohort study.

3. The level of Type I error (α), or the significance level. That is, the probability of finding a significant association when none truly exists (i.e., rejecting the null hypothesis when it is actually correct); or in other words, the probability that observed significant results have occurred by chance. Traditionally, significance levels of 0.05 or less are commonly chosen as the cut-off to minimize the probability that the observed results occurred because of chance.

4. The value of Type II error (β). This is defined as the probability of failing to detect a significant association if one in fact exists (i.e., failure to reject the null hypothesis when it is actually incorrect). Traditionally, β is set at 0.2, a value higher than the level of significance. In choosing α and β, the investigator must weigh the relative disadvantage of falsely rejecting the null hypothesis against missing an effect that is really there. One cannot minimize both α and β simultaneously: as α is decreased, β increases and power declines.

   $1-\beta$ is referred to as the power for a study. Power is the probability of rejecting the null hypothesis (no association) when it is, in fact, false; otherwise stated, it is the ability to detect a true effect of a specified magnitude. In some instances, the investigator may have a limited sample size. By specifying the sample size, he can then calculate the statistical power of the study. The power will tell him whether his study has a sufficient chance of finding an association if there is one. Traditionally, a study power of 80% is desirable. The larger the power required, the larger the necessary sample size. Greater protection from failure requires greater effort. Similarly, the smaller the sample size, the smaller the power, i.e., the greater chance of not detecting an effect if there is one.

The above description is a simple sample size and power computation for a study with dichotomous classification of exposure (and disease) for which no stratification to control for confounding is needed in the analysis. Sample size computation allowing for control of confounding and/or detecting dose response requires fairly sophisticated analysis and is not within the scope of this report.

3.9 Criteria for Causality.

In an epidemiologic sense, causality is a difficult and subtle concept. However, the epidemiologist may take a more pragmatic approach, evaluating whether the evidence suggests that an exposure increases risk of a specific disease and whether or not this evidence is sufficient to support public health action, such as changing recommendations to physicians and patients and to occupational experts, disseminating warning information, or withdrawing a drug or procedure from practice.

Study validity. The first question is whether or not the individual studies have major threats to validity, of the type discussed above. All studies will have limitations, but it is important to identify major problems that cast doubt on all study findings. Temporal sequence, that the exposure precedes the disease, is obviously necessary to establish in a valid study. This has been considered a separate criterion for causality in the past, in part because of the more frequent use in the past of cross-sectional or ecological designs, where, unlike a good cohort or case-control study, temporal sequence may be ambiguous.

Strength of association. Most spurious associations reflect the indirect effects of a true risk factor; these indirect effects usually are substantially smaller than the original risk factor effect. Thus, the larger the association, the less likely it is to be due to such causes. For example, it is very difficult to postulate credible scenarios whereby other factors could explain a 30-fold increased risk of Reye's syndrome in aspirin users. In contrast, many factors could plausibly explain a mortality relative risk of 1.2 in persons undergoing a prostate operation.

Consistency of association. As in other areas of science, confidence in a finding is increased if it is consistently observed in multiple studies performed in different settings.

Biological plausibility. Associations which are biologically implausible should be viewed with more skepticism. For example, it is very unlikely that very brief exposures (such as one month of oral contraceptive use) will increase risk of chronic diseases such as breast cancer. Occasionally, associations that initially appear to be biologically implausible may subsequently become plausible because of new insights into the disease process. For example, the cigarette smoking-lung cancer relationship was initially considered by some to be biologically implausible until carcinogens were identified in cigarettes.

Dose-response. Although helpful, dose-response curves may not always be present over the range of exposure studied. Furthermore, spurious dose-response curves can result from confounding[10] or other study problems.

4. Requirements for a Valid Cohort Study

The requirements for a valid cohort study include specification of the cohort, definition and measurement of exposure, measurement of confounders, ascertainment of disease (outcome), and adequate sample size for analysis. Table 4-1 lists the steps and potential problems in the conduct of cohort studies.

Table 4-1 Problems of cohort studies

Step	Problem
Specification/ Follow up	External Validity Loss to follow up
Exposure	Baseline Misclassification Change during Follow up
Confounders	Measurement Missing/ inadequate
Disease ascertainment	Specificity: Misclassification Sensitivity: Selection Bias
Analysis	Sample Size

4.1 Cohort Specification.

External Validity. A primary issue in selection of the cohort is the tradeoff between the need to identify persons willing to participate and capable of providing good data and in whom there is a reasonable likelihood of detecting an effect versus the need to have a representative sample of the exposed population. In the Hanford Thyroid Disease Study (HTDS), the investigators decided to study a cohort of infants and children who were at risk of ^{131}I exposure because they felt, among other reasons, that this group had the greatest likelihood of showing excess thyroid disease, if there was one. However, one can question the relevance of these findings to adults who were exposed. Similarly, findings from studies of Medicaid populations (which are atypical from the general population, see Section 4.3) may not be generalizable.

Loss to Follow up. If cohort members are lost to follow up, then rates of loss may be associated with exposure status (e.g., radiation exposure). Such differential loss to follow-up can introduce selection bias. With this concern in mind, researchers made extensive efforts in the HTDS to identify and locate study subjects[11].

4.2 Exposure.

Accurate measurement of exposure is crucial for any epidemiologic study. If subjects are inaccurately classified by their exposure status at baseline (misclassification) or if the status changes (e.g., a study of smokers where some quit smoking during follow-up), then the ability to find a true association is reduced. This is a common problem in studies of populations living near nuclear facilities, where geographic distance is used as a surrogate for exposure to radiation. In the HTDS, the investigators are estimating individual radiation doses based on sophisticated

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The material in this section has been adapted from "Pharmacoepidemiology Notes" by Wayne A. Ray, Ph.D., Department of Preventive Medicine, Vanderbilt University School of Medicine

dosimetry. These estimates are derived from questionnaire data on milk consumption, dietary habits, life style factors and life time residences which are then incorporated into dosimetry models developed by the Hanford Technical Dose Reconstruction Study. To allow for inherent uncertainties of the different model parameters, a range of doses using uncertainty analysis is estimated for each subject.

Table 4-2 The Hanford Thyroid Disease Study (HTDS)

Design	Retrospective cohort
Cohort specification/follow up	All live births between 1940-1944 in Benton, Franklin and Adams counties of Washington State, N=3,200
^{131}I exposure	Questionnaire data on diet, residence, and life-style incorporated into radiation dose algorithm developed by the Hanford Technical Dose Reconstruction Project to estimate individual radiation dose with a range of dose uncertainty values.
Potential Confounders	Demographic characteristics, exposures to medical radiation (diagnostic and/or therapeutic) through medical interviews and medical records.
Disease ascertainment	Comprehensive medical examination primarily of the thyroid by endocrinologists including diagnostic procedures; and medical records
Analysis	Person-time. Cumulative incidence, relative risks, separately for male and female

Other problems of exposure that one needs to be aware of and address, if possible, include its nature (type of radiation), timing, and duration. Because baseline exposure status in a cohort study is measured before development of disease, measurement errors will generally result in nondifferential misclassification. This nearly always has the effect of biasing towards the null[12], obscuring true differences between the exposed and unexposed groups. Table 4-2 describes the different elements of HTDS.

4.3 Confounding.

Definition Confounding is "the distortion of a disease/exposure association brought about by the association of other factors with both disease and exposure"[13]. The word *confound* derives from roots meaning "to mix together"; it also has the sense of confusing or misleading. Both of these apply to epidemiologic use of the term, where the effect of some extraneous factor is mingled with that of the exposure of interest, misleading or confusing the investigator. For confounding to be present, the confounder must itself be a risk factor for the disease (or serves as a proxy measure for unknown or unmeasured causes). However, more is required. The confounder must also be associated with the exposure in the cohort or study base.

For example, in cohort studies of lung cancer, smoking is an important confounder. In studies of cholesterol and heart disease, obesity and smoking are confounders because they are not only predictors of heart disease but also related to cholesterol levels (i.e., smokers and obese persons because of their life-styles may have higher cholesterol level). Age and gender can be potential confounders because they are generally related to exposure status and risk of disease.

Management of Confounding Potential confounders are usually controlled for in the study design or during analysis. Statistical techniques, such as stratification or multivariate analyses are appropriate analytic techniques. In the HTDS, the investigators are collecting data on potential confounders, such as basic demographic characteristics and exposure to medical radiation.

4.4 Disease Ascertainment.

Specificity: Misclassification of Disease-Free Persons This type of misclassification occurs when the method used to ascertain disease (or identify cases) incorrectly includes persons without disease. This is a failure of the method's *specificity* because it cannot correctly identify disease-free persons. This failure is reflected in a low proportion of putative cases who actually have the disease, i.e., a low positive predictive value. If this misclassification is random, its effect will be to reduce relative risk. If this misclassification is differential, bias may be introduced.

This type of problem is most common in studies from automated databases (see Section 4.3), where for logistic reasons it may be difficult to obtain access to additional information required to confirm disease occurrence. Validation studies may be helpful.

Sensitivity: Incomplete Identification of Persons with Disease This type of misclassification occurs when the method used to ascertain disease (or identify cases) have poor sensitivity or there is incomplete identification of all cases of disease occurrence in the cohort. For example, in a retrospective cohort study of childhood cancer and maternal medication use in a cohort of 252,000 Tennessee children, the number of cancers occurring in those who migrate out of state is not known. This could potentially bias the results of the study if children who were exposed to the drugs of interest were more likely to migrate than those who were not exposed.

In cohort studies, the primary reasons for missing cases are 1) incomplete follow up, missing disease that occurs after a cohort member is lost to follow up, and 2) insensitive procedures for case identification.

An attractive, yet potentially misleading, strategy in some epidemiologic studies is using medication-taking as a surrogate for disease status. For many diseases treated on an outpatient basis, drug-use data are a readily available indicator of disease presence. However, for most of these types of conditions, a substantial fraction of cases are undiagnosed or untreated. Furthermore because in most practice settings, there rarely, if ever, are uniform procedures and criteria for diagnosis and treatment of disease, the likelihood of being treated with drug will vary substantially, even among patients with the same level of disease. Factors such as patient beliefs

and attitudes, comorbidities, use of other medications, and physician characteristics all may influence probability of diagnosis and treatment.

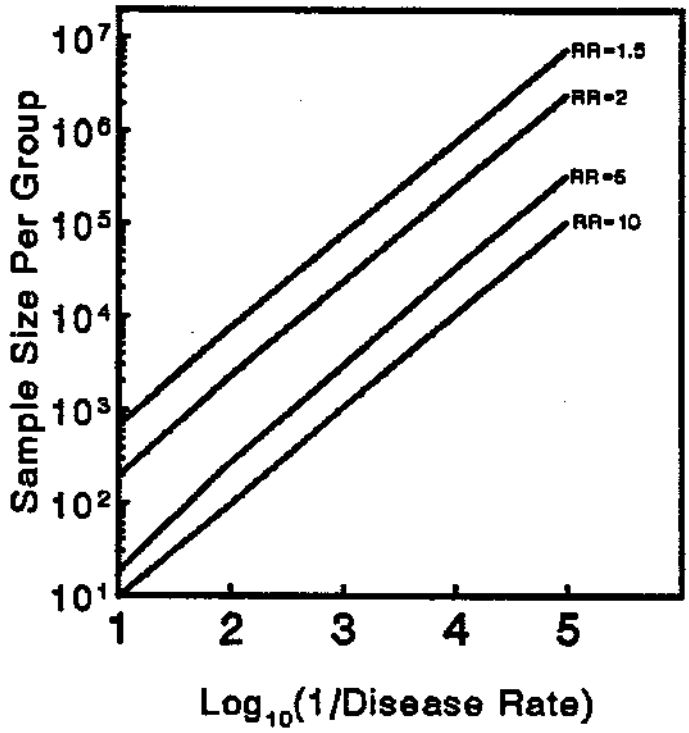
Consider the problem of determining whether certain exposures adversely affect thyroid function. Concerns have been raised that certain calcium channel blockers induce hypothyroidism, leading to the suggestion that this problem be studied by analyzing rates of synthetic thyroid hormone use. Similarly, there is concern that large releases of ^{131}I from nuclear facilities during the 1940s and 1950s may have ablated thyroid function, leading to proposals to compare rates of synthetic thyroid hormone use in affected and unaffected populations. However, hypothyroidism is substantially underdiagnosed. Thus, use of drug as a surrogate for disease could result in findings biased by factors that lead to diagnosis and treatment(such as concern about radiation effects).

In the HTDS, the researchers have made extensive efforts to 1) identify a high proportion of subjects (over 90% in the Pilot Study), and 2) ascertain disease status by comprehensive medical examinations, including blood chemistry and ultrasonography. Furthermore, they have carefully developed case definitions.

4.5 Sample Size.

A major problem of cohort studies (indeed all studies), particularly prospective studies, is adequate sample size (see Figure 4-1). The disease rates in the x-axis are plotted as the log of 1/disease rate. Thus the numbers 1,2,3,4, and 5 are rates of 1/10, 1/100, 1/1000, 1/10,000, and 1/100, 000. Given 80% power and an alpha value of .05, we can see from the figure that to detect a relative risk (RR) of 1.5 (i.e. a 50% increase in risk), we would need to study a sample of nearly 1000 subjects each in the exposed and unexposed groups (i.e., total 2000 subjects) if the rate of disease is 1/10. On the other hand, we would need to study millions of subjects if the disease rate is 1/100,000, given the same relative risk. We can see that as the relative risk to be detected increases and the disease rate is higher, the number of subjects required grows smaller. For example, if one were interested in studying the risk of amyotrophic lateral sclerosis (incidence rate of 1 per 100,000) following exposure to mercury, one would need to study over one million exposed subjects to detect a two-fold increase in risk (i.e., RR=2). Large studies of this type are very expensive and time-consuming. Thus, it is particularly important to perform careful power calculations when designing a cohort study and to inspect confidence intervals when considering a negative finding.

Figure 4-1 Sample Size Estimates by Relative Risk and by Disease Rate



The material in this section has been adapted from "Pharmacoepidemiology Notes" by Wayne A. Ray, Ph.D., Department of Preventive Medicine, Vanderbilt University School of Medicine

5. Requirements for a Valid Case-Control Study

The requirements for a valid case control study include specification of the study base, disease (case) ascertainment, control selection, definition and measurement of exposure, measurement of confounders, and adequate sample size for analysis. Table 5-1 lists the steps in a case-control studies and potential problems at each step.

Table 5-1 Steps and problems of case-control studies

Step	Problem
Study Base Specification	Availability enumeration Person-time
Disease (Case) Ascertainment	Specificity: Misclassification Sensitivity: Selection Bias Prevalent vs Incident
Control Selection	Randomly sampling study base: Selection bias
Exposure	Information Bias Misclassification (Non Differential)
Confounders	Measurement missing/ inadequate
Analysis	Sample size

5.1 Study Base.

Two basic assumptions of a case-control study are that 1) an underlying cohort (well defined population), from which the cases arise, can be identified; and 2) the controls are a random (possibly stratified) sample of this cohort. If we further assume the disease is rare (<10% rate), and if information is collected from subjects in the same way, case-control studies satisfying 1-2 above are inferentially equivalent to cohort studies; the former samples the non-case population to improve efficiency. Thus, cohort studies are not necessarily superior to case-control studies. Although not made explicit in the above derivation, it also is assumed that exposure can be measured with equal accuracy before (cohort) or after (case-control) the disease has occurred. In many studies, this assumption may be difficult to satisfy.

For every proper case-control study, there is a corresponding cohort study. It often is useful to think about problems, such as complex exposure definitions, in terms of the cohort study, a setting in which they often are easier to understand.

Study Base. The cohort underlying a case-control study is called the *study base*, defined as the population giving rise to the cases or persons who would have become cases had they developed the disease.

In their study of breast cancer and serum organochlorines, Krieger and colleagues[14] explicitly defined their study base as the 57,040 women who had undergone a multiphasic health examination between 1964-1969 including person-time of follow up (Table 5-2). At this stage, they could have used a cohort design, but they chose to do a case-control analysis, to reduce the expense of measuring serum organochlorines in all 57,040 women. Thus, all cases of breast cancer in the cohort during follow up were identified and matched controls randomly sampled from the study base.

The material in this section has been adapted from "Pharmacoepidemiology Notes" by Wayne A. Ray, Ph.D., Department of Preventive Medicine, Vanderbilt University School of Medicine

Table 5-2 Study base for Krieger *et al* breast cancer study

Study Base (N=57,040 women)	Members of Kaiser Permanente, Northern California
	Underwent multiphasic health examination, 1964-1969
Follow up Begins (latest date)	Date following multiphasic helath examination
Follow up Ends (earliest date)	Study outcome event
Cases (N=150)	Histopathologically confirmed
Control (N=150)	Matched for race/ethnicity, date of joining Kaiser Permanent year of multiphasic examination, age at multiphasic examination, length of follow-up after examination, and fre of any cancer at the time of matched patient diagnosis
	Active follow up on case event date (date of cancer diagnosis in case) (index date for matched control)

However, for many case-control studies, (e.g., single hospital) the study base cannot be defined explicitly. The investigator first identifies the cases and then attempts to define the population that, had they been cases, would have been included in the study. For example, if cases are identified at a single hospital then controls are selected from among other cases of disease treated at that hospital. Unfortunately, control sampling done on the basis of medical care use, such as admission for another disease, often is correlated with other exposures. In a hypothetical example of a case-control study of estrogens and myocardial infarction, if trauma--i.e. fracture--controls were used, these controls might have lower levels of estrogens than the normal population (estrogen increases bone mass and has a protective effect on fractures), possibly showing a spurious association. Furthermore, hospitals may serve different populations for different diseases.

5.2 Disease (Case) Ascertainment.

Just as in a cohort study, cases of disease (or a defined random sample) occurring in the study base need to be ascertained with high specificity and sensitivity. Failure to do so will cause the same errors of misclassification and selection bias as occur in cohort studies. Cases should generally be restricted to those newly developing the disease (incident cases); otherwise one is also studying factors associated with survival.

A unique problem in case-control studies is obtaining data for all cases that occur in the study base. In a prospective cohort study, the subjects agree to participate at baseline, prior to the occurrence of any outcomes. This should minimize further attrition due to nonparticipation. However, in a case-control study, the study base may be enumerated, but rarely is there an explicit agreement to participate in the study. Refusal by cases to participate may be related to

exposure status. Thus, high non-response rates or different response rates among cases and controls potentially lead to selection bias. Thus strategies that minimize nonparticipation are needed (one advantage of studies conducted solely with automated databases is that all cases and controls can be included).

In addition to inclusion of only confirmed cases, the time of disease onset needs to be established. Other study variables need to be collected for a time prior to disease onset. In the breast cancer study by Krieger and colleagues (Table 5-2), they ascertained all cases through multiple sources: the Kaiser Permanente Medical Care Program hospitalization records, the 1969 Third National Cancer Survey, and the SEER registry of the San Francisco bay area. They selected only histopathologically confirmed cases. Furthermore, they selected a random sample of 150 cases for their case control study.

5.3 Control Selection.

The most controversial aspect of a case-control study is selection of controls. There is a misperception that the controls should be as much like the cases as possible; however, this is not correct. Ideally, controls must be selected from the same population that the cases arose from, i.e. the controls should be a random sample of the study base, or if this not possible and should also be comparable to the cases in terms of their risk to developing the disease (e.g., in a study of estrogens and ovarian cancer, women with no ovaries would be inappropriate to serve as controls since they are not at risk of developing ovarian cancer. In other words, the controls must be representative of those subjects, who had they been ill, would have become cases.

There are several options for selecting controls (Table 5-3). Note the preferred options are random sampling from a primary study base with a roster, or in the absence of a roster, neighborhood controls. Other options have many problems.

Table 5-3 Options for control selection.

Option	Comment
Random Sampling	Preferred
Random Digit Dialing	Useful for telephone interviews. Problems with lack of phones, non-response, refusal
Neighborhood controls	Expensive Best option if no roster
Hospital	Correlated with exposure
Friend/Relative	Possibly Correlated with Exposure

Hospital controls are problematic in epidemiology. Hospital controls work if the case and control diseases have identical catchments and if the exposure does not influence admission probabilities.

Krieger and colleagues selected a random sample of controls from their study base.

5.4 Exposure.

The same issues of definition and measurement described in Section 4 are present in case-control studies. For this design, the most common method of exposure ascertainment is subject interview. This, in conjunction with the case-control design, poses several very difficult problems:

1. Participation of cases and controls. Needing to complete an interview may reduce participation rates, possibly differentially. Proxy interviews will be needed for dead cases (and possibly for their controls) and for subjects who are mentally impaired (a particular problem for studies of the elderly) or who for other reasons cannot complete the interview. Nonparticipating subjects introduce potential selection bias.

2. Obtaining accurate information on past and present exposure status. Often, interviews are conducted after the exposure period of interest. Subjects may be interviewed well after disease onset and there is possibility of differential recall of past exposures (recall bias).

3. Obtaining information of equal accuracy from cases and controls

When possible, it is best to use data collected before disease onset, at least for a sample validation of the interview procedures.

Other methods of documenting exposure include biological specimens and records documenting exposure (see Section 6.2). A major strength of the Krieger study was their use of stored frozen sera of these women collected at baseline prior to development of cancer to determine the levels of organochlorines. These specimens were available equally for the cases and controls.

5.5 Confounders.

Again, a unique problem for case-control studies is that subjects are entered into the study after the disease has occurred, whereas pre-disease data on confounders are needed. This is particularly troublesome for studies that must obtain biologic measurements. For example, early case-control studies that assessed the role of bone density in hip fractures measured bone mineral content of cases and controls after the fracture had occurred. However, inactivity associated with the fracture hospitalization and recuperation may induce substantial bone loss. Similarly, case-control studies of lipids in cancer found lower cholesterol levels in cases; however, this may have reflected the cancer disease process. Krieger's use of frozen sera collected prior to disease onset minimizes this problem. In addition, she matched her controls to cases on several characteristics,

including race/ethnicity, date of joining Kaiser Permanente, year of multiphasic examination, age at multiphasic examination, length of follow-up after examination, and free of any cancer at the time of matched patient diagnosis.

5.6 Sample Size.

The requirements for sample size determination are similar to cohort studies (see previous section), but in general, the sample size required in case-control studies is smaller, thus making them cheaper. Appendix B consists of selected pages of sample size tables, for quick estimates of sample size. The numbers in the first column labeled R is the relative risk of disease due to exposure that one regards as scientifically or clinically important to detect. The other column headings list the number of study cases (and an equal number of controls) needed depending on frequency ('f') of exposure in the general population (or the controls). This table assumes a two-sided level of significance of 0.05 and a β of 0.20 (or a power of 80%).

For example, for a case control study of mercury exposure and its association with amyotrophic lateral sclerosis (ALS) where the prevalence of mercury exposure above a predetermined level in the population is assumed to be 10%, the number of ALS cases required to detect a relative risk of 2 (80% power and an alpha level of .05) is 282 (282 cases and 282 controls). In contrast, if the prevalence of mercury exposure is assumed to be 1%, the number of ALS cases needed is 2394.

6. Inventory of Data Resources for Epidemiologic Studies in Oak Ridge, Tennessee

A central question in all types of epidemiologic studies is where and how to obtain the data needed to define exposure and confounders and to ascertain disease occurrence. Regardless of study design, valid results will depend upon accurate data collection. Sophisticated designs and statistical analysis cannot compensate for low quality data (garbage in- garbage out). Thus, this aspect of a study should always receive very careful review.

Although it would be virtually impossible to catalogue all potential sources of data, there are two broad classes of data: a) those obtained directly from the subjects for the purposes of the study and b) those obtained from records collected for other reasons (e.g. birth and death certificates, occupational records). The appropriate sources of data depend almost entirely upon a study's objectives and resources. Very often, multiple sources are appropriate (i.e. data are collected from the subjects and also records). However, as summarized in Table 4, there are some useful generalizations concerning the advantages and disadvantages of subject contact vs records.

Table 6-1. Relative Merits of Subject Contact versus Records as Data Sources for Epidemiologic Studies.

	Subject Contact	Records
Advantages	More flexible/ precise variable definitions	Accuracy
	Data otherwise unavailable	Completeness
		Lack of bias (generally)
		Less time consuming/ expensive
Disadvantages	Reporting accuracy not always certain	Data availability/suitability
	Reporting bias	Confidentiality
	Low rates of participation possible	
	Time consuming/ expensive	
	Subject inconvenience	

6.1 Data Collection from Subjects.

Keeping the potential disadvantages in mind, all the data needed for an epidemiologic study (for defining exposure, ascertaining disease, and identifying confounders) can be collected directly from subjects. There are many methods for data collection from subjects. Some of these include the following:

1. Interviews (e.g., history of exposure to certain chemicals, eating fish, smoking,

residence history, disease). These can be with subjects or surrogates (not preferred usually).

2. Structured assessments (e.g., developmental scales for infants, mental state examination, depressive symptoms inventory).

3. Physical examination (e.g., muscle strength, blood pressure).

4. Biochemical measurements (e.g., levels of chemicals in blood, urine, or hair).

5. Examination of the environment (e.g., electromagnetic field strength or radon levels in a subject's house).

6.2 Data Collection from Existing Records.

In epidemiologic studies, existing records (automated or manual) can be used to define a study population (e.g. births in a defined area and time), to measure exposure (e.g. medication use from Medicaid pharmacy files, workers exposed to ionizing radiation from occupational records), to ascertain disease (e.g. cancer registry, death certificates), and to trace/locate study subjects (e.g. marriage and divorce certificates, driver license files).

In the following sections, we will briefly describe various records that may be of potential use to future epidemiologic studies in the Oak Ridge setting in four categories: 1) databases of records routinely collected and maintained by the Tennessee State Department of Health and other agencies, 2) databases in the Department of Preventive Medicine at Vanderbilt University, 3) health care provider records (hospital and physician records), and 4) miscellaneous, including national and local databases.

6.2.1 Tennessee State Databases.

Table 6-2 lists the different databases maintained by the Vital Statistics Division of the Tennessee Department of Health, and Tennessee Department of Transportation and Safety. In the following sections, we will briefly describe the databases.

6.2.2 Birth Certificate.

In Tennessee, birth certificates (Appendix C) have been recorded and filed since 1914, but are available in a computerized format from 1959 to the present. In the US, a standardized form with common data elements is used nationally for recording births, with additional data items collected at the discretion of the individual state. There have been several versions of the birth certificates over the years, with newer versions containing more fields for medical data on the mother as well as the newborn. The latest version of the Tennessee birth certificate has been in

use since 1990. Demographic data about the mother, child, and father contained in the birth certificate are useful for tracing individuals and also for serving as the basis in selecting population controls for epidemiologic studies. The current version of the birth certificate, in addition, has a checklist of maternal (medical conditions present in the pregnancy, type of obstetric procedures, progress of labor, and method of delivery) and newborn conditions (birthweight, medical conditions, and congenital malformations) to record their presence. These data could provide good information for understanding maternal and infant issues, and also help in ascertainment of newborn conditions in a population, such as congenital malformations and preterm births. However, the quality of data recorded in the birth certificate varies with different data items. For example, birth weight is generally accurately and consistently recorded; gestational age on the other hand is very subjective and not clearly recorded.

Piper and colleagues from Vanderbilt University did a validation study of the birth certificate information in Tennessee[15]. She compared information reported on the 1989 Tennessee birth certificates with the same data obtained from an ongoing case control study where trained nurse abstractors using a structured data collection instrument reviewed the delivery hospital medical records of mothers and infants. They found that the most reliable information obtained from birth certificates were descriptive demographic data and birth weight. The quality of information obtained from the check boxes in the birth certificate varied widely (see Appendix D). Consistent with other studies, routine medical procedures were better reported in the birth certificates than relatively uncommon conditions and occurrences, even serious ones. Abnormal conditions of the newborn were poorly reported in the birth certificates or not reported at all (fetal alcohol syndrome). Congenital anomalies of the newborn were seriously under reported on birth certificates. The authors concluded with the need for caution in using birth certificate data for assessment of maternal medical risk complications of labor and delivery abnormal conditions of the new born and congenital abnormalities.

6.2.3 Death Certificate.

In Tennessee, death certificates (Appendix E) have been recorded and filed since 1914, but are available in computerized format from 1949 onwards. In the US, a standardized form with common data elements is used nationally for recording deaths, with additional data items collected at the discretion of the individual state. Because demographic characteristics of the deceased subjects (namely their name, address, age and gender, and the underlying cause of death) are recorded in the death certificate, it serves as the basic document for all mortality data. The underlying cause of death is a very useful data item for enumerating cause of mortality in a given population by different personal characteristics. Mortality data have been widely used to generate epidemiological hypothesis because they are processed regularly and therefore are inexpensive and convenient to use, death certificates are required by law when death occurs thus ensuring complete ascertainment, and because mortality trends can be studied because of the availability of these data for many years. Death certificate data are also a useful source for

Table 6-2 Summary of Tennessee Databases Potentially Useful in Subject Tracing and/or Disease Ascertainment

Data Source/Type	Year Started	Year Automated	Data Items				Potential Uses		Comments
			Name	Date of Birth/Age	Sex	Address	Subject Tracing	Disease Ascertainment	
Birth Certificates	1914	1959	✓	✓	✓	✓	✓	✓	Filed ≥ 1914
Death Certificates	1914	1949	✓	✓	✓	✓	✓	✓	Filed ≥ 1914
Fetal Deaths	1960	1973	X	✓	✓	✓	✓	✓	Indexed since 1960 (only name of mother)
Cancer Reporting System	1986	1986	✓	✓	✓	✓	✓	✓	Reliable data from 1989 after mandatory reporting law passed. Quality assessment ongoing.
Birth Defects Registry	1991	1991	✓	✓	✓	✓	✓	✓	Ascertained from multiple existing databases. Quality assessment ongoing.
Hospital Cost Containment System	1990?	1990 ?	X	✓	✓	✓	X	✓	Identifiers not available, however medical record number in UB-92 form can allow tracing back to get records.
Newborn Screening Program	1968	1991	?	✓	✓	✓	✓/X	✓/X	Logistics setup for specimen collection potentially useful for future studies
Marriage Certificates	1790*	1970	✓	✓	✓	✓	✓	X	Useful in identifying name changes. Reliable automated data from 1973.
Divorce Certificates	1900s*	1970	✓	✓	✓	✓	✓	X	Useful in identifying name changes. Reliable automated data from 1973
Vehicle Registration	1964**	1984	✓	✓	✓	✓	✓	X	Current files (i.e. active in past 3 years) contain up to 8 million records. Prior records are in microfiche.
Driver's Licensing	1964**	1984	✓	✓	✓	✓	✓	X	Useful for tracing individuals
U.S. Census (TN)	1790	1970, 1980, 1990	✓	✓	✓	✓	✓	X	Requires special access for getting identifying data.

✓= Yes X= No * Approximately. Varies by county. ** Records available from this year on.

ascertaining endpoints in a defined cohort and for tracking vital status of individuals participating in a study.

The usefulness of death certificate data as an indicator of disease frequency in a population varies largely on the disease being studied. Diseases with high case fatality rates, those that are rapidly fatal and those that are relatively easily diagnosed are most likely to be recorded accurately on a death certificate as an underlying cause of death. For example, lung cancer will usually be recorded accurately whereas chronic bronchitis may not be because it is not fatal. Diabetes may contribute to death eventually but is usually not cited as a cause of death, so a frequency study of diabetes based on mortality data will clearly underascertain the actual frequency of diabetes in the population studied. Other problems associated with mortality data being used for epidemiologic purposes include variable quality and/or careless certification of cause of death (e.g., in rural areas with few physicians, death may be certified by a coroner), incorrect assignment of cause of death codes and changes in rules for assigning these codes over time. Variations in the quality of medical care among regions and time periods can also make comparisons difficult. Thirty years ago, acute childhood leukemias were almost always fatal, but now with recent medical advances, survival is above 70%. Thus, use of death certificates in a study of childhood leukemia currently would seriously underascertain cases of leukemia. To the extent possible, it is important to validate the cause of death with alternative data sources (e.g., verify a sample of death certificates with hospital records) in conducting epidemiologic studies. For the reasons described above, it is important to interpret results of ecologic mortality studies with caution!

6.2.4 Fetal Death.

In Tennessee, a fetal death certificate is filled out following the death of a fetus a) weighing 500 grams or more or b) in the absence of weight, having a gestational age equal to or greater than 22 weeks. Induced abortions are excluded from the fetal death count. Although fetal deaths in Tennessee have been reportable since 1960, computerized fetal death certificate data are available on computerized tapes from 1973. Prior to 1973, only mother's name was available in a computerized format. Fetal death certificate data may be useful in ascertaining cases in studies of adverse pregnancy outcomes. However, in general they are not particularly useful for epidemiologic studies. In many early fetal deaths, the pregnancy may not even be recognized. Many such pregnancies may terminate early and not reported because the mother may not seek medical care. The reporting of specific congenital malformation in fetal deaths is unreliable because the fetus is usually too small and it is difficult to identify such abnormalities in a young fetus.

6.2.5 Tennessee Cancer Reporting System (TCRS).

The TCRS already is and will be an invaluable resource for measuring cancer incidence and monitoring for unusual trends and patterns for the population in Tennessee, and for

generating hypotheses for epidemiologic studies. It will be an excellent source for case ascertainment and for determining cancer endpoints in specific epidemiologic studies. The TCRS was set up following legislation in 1983 that made cancer a reportable disease in Tennessee. Tennessee hospitals and laboratories that diagnose and/or treat cancer are to the report cases to the Department of Health. The purpose of this reporting is "to the insure an accurate and continuous source of data concerning cancer and certain precancerous and tumorous diseases, and to the provide appropriate data to the members of the medical, scientific, and academic research communities for purposes of authorized institutional research." By law, all cases diagnosed after January 1, 1986 are required to the be reported.

Hospitals are required to the report information regarding each patient seen for cancer diagnosis and/or cancer-directed treatment to the TCRS using a standard abstract form (Appendix F). Hospitals are required to submit reports, quarterly, even if they did not see any cases. All cancers, regardless of method of confirmation, are reportable.

The data items collected in the TCRS abstract are consistent with the minimum data requirements established by the American College of Surgeons for hospitals with approved cancer programs to collect and maintain on every cancer seen in the hospital. Additional data collected in the TCRS abstract form include occupation, industry, family history of cancer, and tobacco use.

Procedures to ensure completeness of case ascertainment, unduplication of multiple reports for the same individual from multiple institutions, and ensuring accuracy of diagnoses (a small rural hospital may make a tentative diagnosis, and a larger referral hospital to which the patient is referred may make a more definitive diagnosis, different from the referring hospital) and other data elements are in place. Furthermore, the Department of Health has contracted with The Center of Epidemiologic Research of the Medical Sciences Division of Oak Ridge Associated Universities (ORAU) for an ongoing quality assessment and control study of the TCRS, funded by the current DOE grant.

Although TCRS began data collection since 1986, all hospitals were not compliant in reporting. However, after passage of state legislation instituting penalties for non-compliant institutions, reporting compliance has much improved after 1989. Reliable cancer data are available from 1988 onwards. The TCRS has an advisory body which reviews and decides on applications from researchers and other individuals requesting access to data for studies.

6.2.6 Hospital Cost Containment Information System.

The Hospital Cost Containment Information System has been collecting data, primarily to be able to compare and monitor charges among Tennessee hospitals, reported to the State by private third party payers. However, effective 1994, data from Medicaid and Medicare and also private payors will be included. The data are recorded on the UB-82 (Appendix G) claims for services provided by Tennessee hospitals, and cover all paid inpatient and outpatient claims. Although the first computerized data processed were for calendar year 1990, reliable data are available from 1992. The data in the UB-92 form include the name of the hospital, patient demographics, patient city, county and zipcode of residence, charges for services, diagnoses,

procedures, DRG's (diagnostic related group), admission and discharge dates, and attending physician data. The only identifier in the record is a hospital patient control number. This number is assigned by the hospital to the patient and is unique. However, patients seen at multiple institutions have different numbers. Thus, these data are limited to providing accurate frequencies and patterns of disease based on claims, but not individuals. On the other hand, these data could be an invaluable asset for epidemiologic studies if individuals with a given disease could be identified and then, by using the patient control number, their medical records accessed for verification of demographic and diagnostic data. Currently, these data are being used to identify children included in the birth defects registry. The patient control number can be used to identify the record in the hospital and provide additional identifiers which will allow merging of these data with birth certificate data after the hospital review if it was not possible to match the record prior to the hospital review. However, for confidentiality and privacy reasons, whether identifying data will be available for researchers is unclear.

6.2.7 Tennessee Birth Defects Registry.

The Tennessee Birth Defects Registry is a population-based, statewide registry covering birth defects occurring to infants of residents of the State in a given year. The surveillance system is a passive one which relies on existing databases in the Tennessee Department of Health to identify cases of birth defects. All cases identified from these databases are verified prior to inclusion in the Registry. The first year of data includes infants born to Tennessee residents during 1991.

The goals of the Registry are monitoring birth defects to detect changes or unusual patterns in incidence that may suggest an environmental influence, developing hypotheses for analytical epidemiological studies related to birth defects, and planning and evaluating services available to infants and parents of infants with birth defects.

The databases from which cases of birth defects are being identified include 1) Vital Records data, including birth certificate, death certificate, and fetal death report files, 2) Tennessee Medicaid Management Information System enrollment files and claims for infants with birth defects, 3) Children's Special Services files providing information on children with diagnoses of birth defects or disabilities that entitle them to services directly provided or funded by the State, 4) State laboratory newborn screening data, including results of laboratory tests for phenylketonuria, hypothyroidism, galactosemia, and sickle cell anemia which are required to be performed on every child born in the State, and 5) Hospital Cost Containment Information System data, providing data on diagnoses and procedures related to birth defects based on hospital insurance claims data.

With the exception of some Hospital Cost Containment Information System data and the fetal death files, all of the cases in the Birth Defects Registry include demographic and medical data obtained from the infants birth record. The Cost Containment Information System does not include patient names, but it does include a patient control number which is the same as the patient's medical record number located at the hospital where the information originated.

The Cost Containment database is of great importance to Tennessee's Birth Defects Registry as it is the only source of data to identify birth defects cases not found (1) during newborn screening prior to completion of the birth certificate (2) as a result of health department service delivery, or (3) as a result of receiving Medicaid assistance. The Children's Special Services database is the only source of information for cases with defects that were neither identified at birth nor subsequently hospitalized.

The Department of Health has contracted with The Center of Epidemiologic Research of the Medical Sciences Division of Oak Ridge Associated Universities (ORAU) for a verification and case ascertainment study of the registry cases. All potential cases are verified through review of patient hospital medical records in hospitals across Tennessee. In addition, medical records related to other adverse reproductive outcomes including fetal deaths, infant deaths, and very low birth weight infants of Tennessee residents are reviewed, even if the fetal death report, death certificate or birth certificate does not mention any type of defect. The study began in late 1993.

Cases in the Birth Defects Registry include all defects diagnosed up through age one. Diagnoses included in the Registry are the majority of the defects are International Classification of Diseases (Ninth Revision) codes 740.0 to 759.7. Each birth defect is classified as major or minor, with registry cases being limited to the major defects. Major birth defects are defined as those that affect survival and require substantial medical care or result in marked physiological or psychological impairment. Birth defects defined as "minor birth defects" are included only if they occur in combination with a major defect.

6.2.8 Newborn Screening Program.

As required by law, the State Laboratory Newborn Screening Program collects data on infants who are screened for phenylketonuria (PKU) (since 1968), hypothyroidism (since 1980), hemoglobinopathy (since 1988), and galactosemia (since 1992). Although data have been computerized since 1990, reliable data are available from 1991. By law, specimens are kept for six months, and records for up to two years. The established logistics of collecting specimens from all birthing facilities in this program may be useful in providing support for specimen collection for an epidemiologic study of newborns.

6.2.9 U.S. Census.

The Census Bureau counts the population living in every State in the United States once every 10 years, and collects general demographic data for everyone, and data on social, housing and economic characteristics for a sample. Based on socio-economic characteristics, the Census divides localities by census tracts. For epidemiologic studies, the census tract is a useful surrogate for socioeconomic status of individuals, an important variable that may influence rates and distribution of disease. Although the Census Bureau has individual identifiers that would be useful in tracing individuals, the public versions of the data tapes do not include these items.

6.2.10 Marriage/Divorce Registration.

All marriages and annulment of marriages in Tennessee must be registered. Since 1970 marriage and divorce certificates in the state are available in a computerized format. The certificates (Appendices H and I) contain demographic data on the individuals, such as name, date of birth, gender and address. This is a useful source of data for tracing or locating subjects and also by helping to identify changes in surnames of women. The Hanford Thyroid Disease Pilot Study found this database a useful resource in identifying female subjects, especially those with surname changes.

6.2.11 Vehicle Registration/Drivers License.

Since 1984 the Tennessee Department of Transportation and Safety has computerized records of all vehicles that are registered in the state and also of all licensed drivers. These files (Appendix J) contain demographic characteristics of individuals, specifically their name, gender, date of birth, and residence. The Tennessee vehicle registration files contain up to 8 million active records. These records are very useful in tracing and identifying subjects, since most adults have registered vehicles and/or drivers license. The Hanford Thyroid Disease Pilot Study identified 33% of their subjects through this source.

6.3 Automated Databases at Vanderbilt University.

Automated databases, such as Tennessee Medicaid, arise from systems for providing medical care for defined populations. For administrative or medical records reasons, records of encounters between patients and health care providers are kept. Using Tennessee Medicaid files and linking with other Vital Statistics files (birth, death, fetal death files), the Department of Preventive Medicine at Vanderbilt University has set up and maintains a unique record-based system which has the potential capacity to support entire epidemiologic studies, providing data on exposure (such as drugs) and outcomes (illness), and on some confounding variables.

Medicaid is a federal-state program for provision of health care to qualifying poor in the U.S.[16]. It initially provided benefits to persons already eligible to receive benefits under other Federal assistance programs, primarily Aid to Families with Dependent Children and Supplemental Security income for the disabled, blind, and aged, or to persons who are "medically needy"; i.e., they are in the appropriate category for one of the federal assistance programs and, after adjustment for medical expenses, have an income that meets program guidelines. In recent years, coverage has been extended to other groups, most notably low-to-moderate income women giving birth. The federal

Table 6-3 Tennessee Medicaid Population, 1990

Group	N	% State
All	583,000	12
Births	30,000	46
Age ≥65	109,000	20
Age ≥85	24,000	36
Nursing Home	20,000	67
Afro-American	217,000	28

government regulates program eligibility and benefits and pays a substantial share of costs (in Tennessee, 70% of care and 50% of administrative costs). However, the states administer Medicaid programs and can exercise many coverage options.

Medicaid enrollees are not a random sample of or even a representative selection of the U.S. population. Indeed, it is helpful to think of Medicaid as distinct populations: 1) pregnant women, 2) infants and children, 3) young mothers, 4) disabled and blind, and 5) the aged. Table 6-3 illustrates this point, showing how the Tennessee Medicaid population differs from that of the state [17].

Thus, Medicaid is particularly well suited to study infants, the elderly, persons in nursing homes, and African-Americans. Conversely, Medicaid is poorly suited for study of some populations, such as middle aged males [17].

Another characteristic of Medicaid if that eligibility status can change. Thus, there may be only a limited amount of follow up available for a substantial population of enrollees, particularly those who are younger [17].

Medicaid has traditionally allowed enrollees to select health care providers and then has reimbursed providers for services performed. This process generates *claims files,* which are computerized abstracts of provider bills. Table 6-4 shows the number of Medicaid enrollees in Roane county, Anderson county and fourteen surrounding counties.

In the following sections, we briefly describe some of the files and data elements of the Tennessee Medicaid database. A summary of the data files is presented in Table 6-5.

Table 6-4 Population, Number and Proportion Enrolled in TN Medicaid in Roane County, Anderson County, and 14 Surrounding Counties

County	Population (1990 Census)	Medicaid Enrollees (1993)	
		Number	% of County
Anderson	68250	9857	14.4
Blount	85969	10281	12.0
Campbell	35079	9897	28.2
Cocke	29141	6779	23.3
Cumberland	34736	5443	15.7
Grainger	17095	3372	19.7
Knox	335749	43847	13.1
Loudon	31255	3947	12.6
McMinn	42383	6212	14.7
Meigs	8033	1504	18.7
Monroe	30541	6226	20.4
Morgan	17300	3398	19.6
Rhea	24344	4814	19.8
Roane	47227	7486	15.9
Scott	18358	5970	32.5
Union	13694	2702	19.7

Table 6-5 Overview of Tennessee Medicaid database.

File	Medicaid Function	Primary Use in Epidemiologic Studies
Enrollment	Registry persons who can receive benefits	1. Defines population/study base for cohort/case-control studies 2. Demographic characteristics 3. Identifiers for linkages
Pharmacy	Claims for filled prescriptions	1. Drug exposure ascertainment 2. Health status indicator
Inpatient	Claims for hospital stays	1. Disease ascertainment 2. Health status indicator
Outpatient	Claims for emergency room, outpatient clinics, physicians, and other ambulatory care providers	1. Disease ascertainment 2. Health status indicator
Nursing home	Claims for nursing home stays	1. Identify nursing home residents 2. Health status indicator
Linked Files: Medicare Vital records Mothers-children Health clinics Driving files Cancer registry		Hospital, outpatient information ≥65 Deaths and births Fetal exposures to prescription drugs Childhood immunizations Population, outcomes for crash studies Cancer outcomes

elements in the enrollment file are included in Table 6-6.

Pharmacy File. The pharmacy file includes records of prescriptions dispensed at the pharmacy. In addition to the recipient number, provider number, physician number, and prescription date, it includes name of drug, dose, and days supply filled. This file is crucial for pharmacoepidemiology because it is a source of drug exposure data.

Inpatient File. The inpatient file has records of hospital stays for which bills are submitted (Table 6-7). This file is valuable in ascertaining outcomes in epidemiologic studies.

Outpatient Files. The outpatient files contain records from visits to hospital emergency department, outpatient clinics or surgical facilities, and other care providers. These files may be useful for case ascertainment or for defining confounders.

The primary reason for incompleteness is failure of providers to submit bills. There are service limitations. While procedures are generally precise and accurate, diagnostic data usually requires verification. For facilities such as hospital-based clinical or outpatient surgical facilities, at least two claims will result from each encounter: one for the use of the facility per se (clinic claim) and the second for the professional service (physician claim).

Table 6-7 Tennessee Medicaid Inpatient File Data Elements

Element	Description/Comment
Recipient Number	Unique ID
Provider Number	Hospital
Admission Date	
Discharge Date	There may be multiple claims for one stay
Diagnosis	Medicaid only: Primary and secondary discharge Medicaid-Medicare: Admitting and 5 discharge All Coded ICD-9-CM
Surgical procedures	ICD-9-CM
Fiscal Data	Charges and Reimbursement

Linkage Files. In Tennessee, we have linked Medicaid data to multiple other sources (Table 6-8). These linkages use probabilistic computerized algorithms that score the quality of the match between pairs of records from the files being linked and keep as matches those with scores exceeding a predetermined cut point. If demographics, full name, and birth date are present in both files, the quality of the link is quite good, typically fewer than 1% false positives (99% positive productive value) and sensitivity of 90% or better. Sensitivity improves as additional data elements for linkage are available.

Tennessee Childhood Cancer Database. The Department of Preventive Medicine at Vanderbilt University has established a TN childhood cancer database for **children born on or after January 1, 1975.** It was set up as an integral component of an ongoing study of maternal medication use and subsequent risk of childhood cancer in a cohort of children born between January 1, 1975 and December 31, 1991 to women enrolled in TN Medicaid. The database is thus limited to children born after January 1, 1975 to coincide with the start of the Medicaid program.

The database includes all cases of childhood cancer first diagnosed between January 1, 1975 and December 31, 1992, primarily from the medical records/logs/indices/computerized files of Vanderbilt University Medical Center in Nashville, St. Jude Children's Research Hospital and LeBonheur Children's Hospital in Memphis, East Tennessee Children's Hospital and the UT Medical Center in Knoxville, Erlanger Medical Center in Chattanooga, and the Johnson City Medical Center Hospital in Johnson City. In addition, the database was supplemented with data from the TN Cancer Registry for 1987 through 1992.

Data elements in the database include child and parent's names and address, demographic information (date of birth, gender, state of birth), date of diagnosis and institution making the diagnosis, and cancer type. Completeness of case ascertainment for the database was evaluated by comparing cases from the database with records of Tennessee death certificates with cause of death listed as cancer and also with Tennessee Medicaid enrollment files for children listed with a cancer diagnosis.

Table 6-8 Linked Tennessee Databases at Vanderbilt University Potentially Useful for Epidemiologic Studies

Data Source/Type	Years Available	Data Items				Potential Uses		Purpose
		Name	Date of Birth/ Age	Sex	Address	Subject Tracing	Disease Identification	
TN Medicaid	1974-1993	✓	✓	✓	✓	✓	✓	As described earlier
TN Medicaid - Death-Linked Files	1974-1993	✓	✓	✓	✓	✓	✓	Person time, outcome ascertainment
TN Birth-Death-Fetal Death-Linked Files	1974-1993	✓	✓	✓	✓	✓	✓	Establish vital status
TN Medicaid-Maternal-Child-Linked Files	1974-1993	✓	✓	✓	✓	✓	✓	Establish natality, gestational age, prenatal age, fetal exposure, maternal characteristics
TN Childhood Cancer Database	1975-1993	✓	✓	✓	✓	✓	✓	Useful for study of childhood cancer epidemiology
TN Childhood Cancer-Birth-Death-Fetal Death-Linked Files	-17	✓	✓	✓	✓	✓	✓	Study of birth characteristics as risk factors for cancer; establish vital status
TN Medicaid-Maternal-Child-Childhood Cancer Linked Files	1975-1993	✓	✓	✓	✓	✓	✓	Fetal exposures to prescription drugs and maternal characteristics in etiology of cancer

✓= Yes X= No

The records in the database were linked to TN birth certificate files to identify those cancer cases who were born in Tennessee state during the study period. For these cases, the database in addition contains all data elements available in birth certificates. In the Oak Ridge setting, this database would thus be useful in studies trying to identify cancer cases in children born in this area (county of birth) from 1975 through 1992. Furthermore, this database can be continually updated with data from the TN Cancer Registry, thus increasing its value in the coming years.

Data Quality. Medicaid data are routinely audited by the Health Care Financing Administration, which insures a certain level of data quality. The audit is most stringent for data elements related to payment, such as specific drug, procedure performed, provider, etc.

Although the inpatient diagnosis and procedures provide a starting point for case ascertainment, this usually requires review of medical records. Table 6-9 shows the process of case ascertainment in a study of upper gastrointestinal bleeding and NSAID use. Note that in the final study, only one third of the original cases were included.

Table 6-9. Case Identification Process

Hospital Admission with Screening Diagnosis	4097
Technical Exclusions	582
Record Unavailable	252
Illness During Hospitalization	245
Event did not meet enrollment date/age criteria	85
Diagnostic Exclusions	1917
Chronic Disease or other known Upper Cause	260
Unknown Site	382
Lower Intestinal	524
Other Upper GI disease	492
Past History only	132
Other Diagnoses	127
Total Confirmed Cases	1598
Disease Onset within 30 days Hospitalization	227
Total Cases in the Analysis	**1371**

Table 6-10 lists some of the strengths and limitations of automated databases for epidemiology. However, the greatest limitation of these databases in the Oak Ridge setting is that they are not available for the periods when the effects of the highest public exposures are most likely to be found.

Table 6-10 Strengths and limitations of automated databases for epidemiology

Strengths	Limitations
Accurate record of exposure (e.g., drugs)	Limited data elements
No exclusions for non-participation	Limited population size
Population-based	Atypical population characteristics/non-generalizability
Comprehensive identification of potential cases.	May not cover period of interest
Timely and inexpensive	

6.4 Health Care Provider Records.

6.4.1 Hospital Records.

Use of hospital records to obtain information on disease occurrence with few exceptions requires reviewing the medical records and abstracting data items that are relevant for the disease under consideration. Hospital records usually have good diagnostic information. The quality of medical information in these records is better than death certificate data. Hospital data are useful for studying diseases that are traditionally treated in hospitals. In using these data, the appropriateness of the disease under study, the appropriateness of the hospital surveyed and the catchment area for the disease need to be considered. For example, cancer is almost always treated in a hospital but mental illness is frequently not. Well defined disease, for example malignant melanoma, is more easy to ascertain than chronic brain syndrome or tremors from medical records. The appropriateness of hospitals surveyed and the catchment area it serves must be considered. For example, to ascertain cases of amyotrophic lateral sclerosis (ALS) in the Oak Ridge population, we would include all hospitals serving this population and/or regional referral hospitals outside this area where such cases might potentially be seen. On the other hand, to ascertain cases of childhood cancer which are generally treated in large, referral institutions, we would target East Tennessee Children's Hospital in Knoxville, Vanderbilt University Medical Center in Nashville and St. Jude Children's Cancer Research Center and Hospital in Memphis. It is also important to try to identify cases from multiple sources within a hospital, and not always rely entirely on discharge diagnostic listing from medical records. For example, malignancies can be ascertained from medical records, tumor registry if the hospital has one, and also from

Pathology laboratory records. It is also important to determine whether hospital records are available for the time period being studied. Other considerations in using medical records are that records may often be incomplete, and the information available may vary by hospital and even by physicians within a hospital. Similarly diagnostic variability may exist among hospitals and physicians.

To evaluate the availability of data in hospitals in Roane and Anderson counties and fourteen surrounding counties, we conducted an informal survey of medical records staff in these hospitals. The results (Table 6.11 and Appendix K) of the survey indicate that only 3 of 22 hospitals had a computerized disease retrieval system using ICD diagnostic codes prior to 1985, and 18 of the 22 after 1985. Prior to computerization, identification of patients by disease could be done by manual review of index cards, microfiche/microfilm, or actual medical records. As seen in Appendix K, the period of availability of such records varied considerably by hospital. Ft. Sanders Loudon Medical Center had microfiche/microfilm records available from 1939 whereas Athens Community Hospital had records from 1981 onward.

Table 6-11 Availability of Computerized Disease Retrieval Systems in Hospitals in Roane County, Anderson County, and 14 Surrounding Counties, by Year of Availability

Years When Computerized Disease Retrieval System Became Available	#	%
≥ 1990	7	32.0
1985-1989	11	50.0
1980-1984	2	9.0
<1980	1	4.5
None	1	4.5
Total	22	100.0

Methodist Medical Center in Oak Ridge had microfiche/microfilm available from 1972 onward. Although the hospital had some records dating back to the early years of its establishment as a Military Hospital, these records were mainly limited to patients who received care after 1972. The hospital had a master card index of all patients (name, date of birth, gender, dates of admission/discharge but no diagnosis) dating back to its early days, although its completeness is uncertain. The medical records staff indicated that if provided with names and other identifying information of individuals, they could determine whether records were available and for what length of time.

However, the major hospitals in Knox County had records dating back to the 1950s or the years they were established. It is reasonable to assume that residents with serious illness, living in the general vicinity of ORR, would have been referred to these centers. These findings indicate that for epidemiologic studies, case ascertainment for illness diagnosed prior to 1985 is feasible though labor intensive. The likelihood of missing records is also of concern, raising issues of possible bias due to underascertainment of cases.

6.4.2 Physician Records.

Records of physicians in office-based or group practice may appear to be a valuable source of data and diseases, especially for diseases treated in physician offices only. However,

obtaining permission for these records is usually very difficult due to privacy and confidentiality reasons. Furthermore, physician records are usually brief, providing limited information on primary symptoms and basic diagnosis and laboratory data and primary diagnoses. In addition, there is great variability in quality of records, and the researcher generally does not have opportunities to validate records. Thus, these records are of limited use in epidemiologic studies. However, for certain diseases (e.g., ALS), which are seen primarily or through referral by specialty physicians (i.e. neurologists for ALS), surveying records of such physicians may be useful. Listings of licensed physicians by specialty practicing in a given area can be obtained from the Tennessee Health Department's Licensing Division, from regional and state medical societies, and also from medical staff listings of the individual hospitals in the area. However, in studies that require ascertainment of diseases that were diagnosed in the distant past, physician records may not be useful. This is mainly because records of physicians who may have retired, deceased, or moved out of the area may not be accessible or may no longer exist. This is particularly true in the Oak Ridge setting, where most of the population exposures occurred over three decades ago.

6.5 Miscellaneous.

Other sources of data include the National Death Index (NDI) which has death certificate data for all deaths in the United States since 1978. With a nominal fee per record, the NDI can identify individuals who have died, provided they receive identifying information on subjects. This is a useful source to identify vital status of subjects in a study who may have migrated to another state and died. The Oak Ridge Institute of Nuclear Studies, now a part of ORAU, has a DOE database of approximately 3,400 individuals, mostly with advanced cancer, who underwent total body irradiation as an investigative therapy from 1950-1972. Although all of these individuals are not from the Oak Ridge area, nevertheless it is a potential source for case ascertainment. The records are being entered into a computerized database. In addition, there are many other potential databases, described by Gable (Appendix L)

6.6 Exposure Assessment for Epidemiologic Studies in Oak Ridge, Tennessee.

In an epidemiologic study, exposure can be assessed in several ways, including geographic/political boundaries to define exposed versus non-exposed populations, dose reconstruction by mathematical modeling, use of biologic markers, subject interviews, and existing records (hospital or occupational). In the Oak Ridge setting, the population exposed could be defined using data from the Dose Reconstruction Study. Data from this study supplemented with data obtained from subject interviews could help define doses to individuals.

Some methods for exposure measurement in environmental epidemiology are briefly described below.

Geographic/political. These methods used to assign exposures are quite crude (pesticide usage patterns, residence near a point of pollution or nuclear facility). This type of exposure definition results in misclassification of exposure and reduces the ability to find a true association.

Dose reconstruction. In addition to the A-bomb survivor studies using individual radiation dose estimates derived from basically a single acute exposure, two published epidemiologic studies[18,19] in residents living downwind from the Nevada Test Site in Southern Utah have estimated individual radiation dose to define exposure. In this type of exposure, there may be multiple pathways by which a person might be exposed and it is important to consider all elements and all routes. For example, residents downwind of the Nevada Test Site could have been exposed to external gamma radiation from the passing fallout cloud itself, from ingesting contaminated milk or vegetables, or, in the case of infants, from *in utero* exposures or breast-feeding. For each of these pathways, several different radionuclides might need to be considered. After eliminating pathways that would be expected to make a negligible contribution to the total dose, one can estimate the likely dose rate per unit of exposure to each pathway. In the fallout example, this involved consideration of 1) source term, the amount and type of radionuclide released; 2) the environmental transport, dispersion from the source to sites of deposition; 3) rate of radioactive decay and environmental dispersion of the radionuclides; 4) farm management practices leading to contamination of dairy cattle or vegetables; 5) estimates of the uptake of radionuclides by vegetables and milk; 6) distribution of milk and vegetables to consumers; and uptake by the target organ from ingesting radionuclides[18,20]. To calculate an individual dose, this information was then combined with extensive questionnaire data on breast-feeding and maternal and individual consumption of milk and vegetables at various ages. For some subjects, modifications were needed to allow for homegrown vegetables or backyard cows or goats. For subjects with incomplete exposure information, distributions of default values specific to the particular circumstances (age, sex, location, etc.) were developed. Similar calculations were performed for each of 100 nuclear tests conducted in the NTS during the mid 1950s. The results then were summed to produce estimates of each subject's total dose[18,20].

The dosimetry methodology, which was essentially developed during the Utah fallout studies, is now being applied in the Hanford Thyroid Disease Study to estimate individual dose. Other DOE facilities where studies are being considered are applying similar methods. In Oak Ridge, the goal of the dose reconstruction study is to provide suitable estimate of doses for a contaminant, provided there appears to have been a significant amount of releases. The initial process will estimate doses to representative individuals in the population. If an epidemiologic study is deemed feasible, then additional data from subjects will need to be collected to estimate individual dose.

There have been no published epidemiologic studies using this methodology to define individual historical exposures to mercury and PCBs. Because of the ubiquitous nature of such contaminants, it is important to carefully validate the models used to estimate such exposures.

Biologic Markers. Because of the difficulty of obtaining accurate and unbiased exposure information from study subjects and the difficulty of estimating the doses that such exposures might produce, there has been great interest in the development of biologic markers. These may be defined as "cellular, biochemical, or molecular alterations that are measurable in biological media, such as human tissue, cells, or fluids"[21]. If used appropriately, biologic markers allow for considerable improvement in measurement of dose. First, they may reduce the errors arising from

subjects' lack of knowledge, memory failure, biased recall, or deliberate misinformation[21]. Second, even when reports of exposure by subjects are accurate, individuals may vary considerably in uptake and handling of material. Errors as a result of such individual variation can be reduced or removed by using markers that provide an estimate of the dose to a particular individual. Another advantage of biologic markers is that generally they give a quantitative, or at least semiquantitative, estimate of dose. Because measurement of biologic markers are often expensive, they can be used as 'gold standards' to validate models or other methods of exposure estimation, thus allowing studies to rely on less accurate exposure measures to reduce cost[21].

To be useful in environmental epidemiology studies, a biologic exposure marker should 1) be clearly better than other measurements; 2) be able to differentiate between exposure levels; 3) be applicable or feasible on a large scale; or if too expensive for wide use, should at least be acceptable to subjects in a validation sub-study. Ideally, before markers are used in epidemiologic research, their sensitivity and specificity should be known from both the laboratory and epidemiologic perspectives. Reliability of results within (intra-observer) and between (inter-observer) laboratories must also be known. Furthermore, the particular time frame they reflect during which they can be measured *in vivo* must be established so that they provide interpretable data regarding time and dose[21].

At present, few exposure markers meet these requirements. Some markers may provide a record of cumulative exposure (e.g. bone lead measurement), but most can assess only relatively recent exposures. Studies of biologic markers that use a case-control design and a cross-sectional marker of exposure can be difficult to interpret because of ambiguity about the temporal sequence of the marker and the disease (e.g., whether selenium levels in breast cancer cases are cause or effect)[21].

Biological markers of exposure to mercury include mercury levels in blood, urine, and hair. For PCBs, markers of exposure include PCB levels in serum, blood and fatty tissues. However, there are no established biomarkers for assessment of historic exposure to mercury or PCBs.

Other. Data on exposure can be collected from subject interviews. An important component of individual dosimetry for ^{131}I exposure is obtaining information on dietary habits, including consumption of milk and leafy vegetables, areas of lifetime residence, and other life-style factors (outdoor activities). Other potential sources include using existing records (hospital or occupational), especially to define past exposures. For example, radiation dose can be estimated for a worker by reviewing worker records. In occupational studies, payroll intervals are used to assemble a job history. The use of records from years past to establish exposure status has the important advantage of alleviating recall bias, although it may introduce its own problem (e.g., missing records and less details in records from early years).

6.7 Disease Ascertainment for Epidemiologic Studies in Oak Ridge, Tennessee.

In an epidemiologic study, it is important to carefully define study end points. In defining study end points, the objective should be to specify the health outcome of interest as precisely as possible. Vague definitions of outcomes may include irrelevant cases, which may dilute the chances of finding associations, especially if they are weak. In fact, ideally one should consider subgroups of disease that are etiologically homogeneous and that are believed to be responsive to the exposure of interest on the basis of theory or prior observations (e.g., certain histopathologic types of lung cancer and radon; leukemia types and subtypes with ionizing radiation and EMFs). However, this may raise a problem of sample size and inadequate power. It is also helpful to try to validate cases with other sources of data. For example, if a subject gives a history of diabetes in an interview, review of medical records could verify this.

The main potential sources of data for disease ascertainment in the Oak Ridge setting include direct subject interviews, provider records, the Tennessee State Cancer Reporting System, the Birth Defects Registry, Birth and Death Certificate files, the Hospital Cost Containment System, and the Vanderbilt databases.

6.8 Identification and Tracing of Study Population for Epidemiologic Studies in Oak Ridge, Tennessee.

There are a variety of sources and methods to identify, locate, and also determine vital status of individuals in epidemiologic studies for which they have to be located after many years of follow-up, either retrospectively or prospectively. Some of the main sources include the State vehicle registration and driver's licensing files, birth and death certificates, marriage and divorce records, old telephone directories and current national telephone directories in CD-rom, and also from relatives. There are special private agencies (such as Equifax) that will trace individuals with good success, but they tend to be expensive.
The HTDS Pilot Study used extensive methods to locate their subjects. Table 6-12 compares some of the methods used by HTDS with their use for future studies at Oak Ridge.

Table 6-12 Availability in Tennessee of Data Sources Used in the Hanford Thyroid Disease Study in Washington State to Trace and Locate Study Subjects.

Data Source	Hanford	Oak Ridge
Death Certificate Files	Y	Y
Birth Certificate Files	Y	Y
Driver/vehicle Licensing Files	Y	Y
Marriage/Divorce Certificate Files	Y	Y
Telephone Directories	Y	Y
CD-rom Telephone Directories	Y	Y
Reverse/city Directories	Y	Y
Family	Y	?
Genealogical Society	Y	N

6.9 Conclusions

The inventory of data sources reviewed in this section suggest that data needed for an

analytic epidemiologic study in the Oak Ridge population are potentially available. Data needed for identifying the population potentially exposed historically to one or more of the contaminants of concern could be available from the current Dose Reconstruction Study. Sampling, tracing and/or locating such individuals can be done using the sources described above, such as use of birth and death certificates, marriage and divorce records, drivers license and vehicle registration records, old telephone directories and current CD-rom telephone directories. Dose estimates to individuals could be calculated with additional information obtained from interview questionnaires. Outcomes can be ascertained directly from subject interview and/or physical examination, review of medical records in hospitals, and death certificates. Automated disease registries, such as the TCRS, the Birth Defects Registry, and the Vanderbilt databases, can be useful sources in screening for potential study subjects who may have been diagnosed with a study disease. However, a major limitation of these registries is that they were established only recently. Thus, they lack data for the period (1950s - 1960s) during which the population was at the highest risk for exposure to the contaminants. Similarly, the completeness and quality of medical records in hospitals of this region for the earlier time period appear to vary by institution. Well defined outcomes, such as cancer, would be easier to ascertain than ill defined ones, such as tremors or neurological deficits. If an epidemiologic study were considered in this population in the future, a pilot phase to evaluate availability and quality of data needed for the specific study should be conducted prior to the main study. Nevertheless, any meaningful study would face considerable logistic challenges and require substantial resources and time to implement.

7. Iodine-131

7.1 Iodine-131: Description.

Iodine-131 is a product of fission of uranium and plutonium and in many situations, is the most important of the iodine isotopes from the view point of environmental contamination and resulting doses to individuals. It has a radioactive decay half-life of 8.04 days and is a beta and gamma emitter. It has been released to the environment as the result of nuclear explosions, and releases from nuclear reactors and fuel reprocessing plants, although it may also be present as a result of spontaneous fission of natural uranium (Table 7-1)[22].

Iodine is metabolized by the thyroid gland, where it is selectively taken up and concentrated. Its concentration in the thyroid gland is several orders of magnitude over the rest of the body, and since the major dose is due to emission of beta-particles which have a short range in human tissues, the absorbed radiation doses in the thyroid are 1000 times higher than in the other organs of the body. It is an essential component of thyroid hormones, which are necessary for growth and metabolism of the body. It is extensively used medically for diagnosis and treatment of thyroid abnormalities[22].

After ingestion, it is rapidly absorbed from the gastrointestinal tract and if inhaled, is also well absorbed from the lungs into the general blood circulation. It is estimated that up to one third of the iodine entering the body is taken up by the thyroid gland and the rest excreted via the kidneys. It is retained in the thyroid for a biological half-life of 120 days, which is age dependent. The amount of iodine uptake in man depends on age and mass of thyroid of individuals, fractional uptake by the thyroid, the effective residence half-time in the thyroid, breathing rate and consumption rate of contaminated foodstuffs. It also crosses the blood/brain and placental barriers[22]. People are exposed predominantly by the air-vegetation-milk pathway.

7.2 Characteristics of Releases from the ORR.

In Oak Ridge, neutron irradiated uranium slugs from the X-10 graphite reactor and also some from the Hanford nuclear facility in Washington state were dissolved in a nitric acid solution to extract radioactive lanthanum for use in nuclear weapons research from 1944-1956. It was estimated from the Phase I Study that up to 300,000 Ci of ^{131}I could have been released, mainly to the atmosphere[1], although recent estimates indicate it could be lower. The off-site population (those living within 20 km [including the city of Oak Ridge] of X-10) living downwind could have been exposed by inhaling the ^{131}I or by ingesting it from food products (especially leafy vegetables), produced locally from soil contaminated by deposition of the ^{131}I. Infants and children who drank fresh milk from cows and goats grazing in open, contaminated pastures would especially be at risk for high exposures. However, the ^{131}I from these releases decayed long ago and presents no risk to the present population.

Table 7-1 Summary of Properties of ^{131}I and Characteristics of Releases from the ORR

^{131}I	
Properties	
Origin	Fission product
Sources from:	Radioactive fallout from nuclear weapons testing Nuclear reactors Fuel reprocessing plants Some from spontaneous fission of uranium in nature
Radiation emitted	Mainly beta and gamma rays
Half-life	8.04 days
Route/pathway of exposure	Inhalation, ingestion (air-vegetation-milk)
Distribution in human body	Well absorbed and selectively taken up by the thyroid
Excretion	Kidneys
Effective biological half-life	120 days
Crosses blood/brain and placental barriers	Yes
Use	Diagnostic and therapeutic purposes
Characteristics of Releases from the Oak Ridge Reservation	
Source/Type	Radioactive Lanthanum Processing in X-10 (ORNL)/ mostly airborne releases
Years of releases	1944-1956
Amount released	Estimated upto 300,000 curies
Population at potential risk	Within 20 km of X-10 (includes city of Oak Ridge)

7.3 Adverse Health Outcomes Associated with Iodine-131.

7.3.1 Thyroid and Parathyroid Glands.

The thyroid is a relatively small (15-20 grams) endocrine gland, located at the base of the front of the neck, which produces thyroid hormones (thyroxine, triiodothyronine) necessary for regulating normal metabolism. Since iodine is essential in the production of the thyroid

hormones, the thyroid gland is extremely efficient in the uptake, concentration, and storage of iodine (including radioactive iodine) that enters the body. Thus, it is a reasonable strategy to evaluate potential adverse health outcomes associated with exposure to radioactive iodine by focusing on thyroid diseases in individuals[23].

The parathyroid glands are tiny glands located just behind the thyroid. These glands produce the parathyroid hormone, which regulates calcium and phosphate metabolism in the body. Because of their close proximity to the thyroid, it is estimated that they may receive up to 30% of the thyroid dose for a given amount of ^{131}I taken up by adjacent thyroid cells[24]. In considering potential health effects associated with thyroid radiation exposure, it may therefore be important to include effects on the parathyroid glands[23].

7.3.2 ^{131}I and Thyroid and Parathyroid Disease.

Radiation-induced diseases of the thyroid and parathyroid glands in humans broadly include thyroid neoplasia (benign and malignant neoplasms), hypothyroidism, and hyperparathyroidism. These conditions are discussed below.

The thyroid glands can be exposed to external photon (gamma or x-radiation) or internal radiation from beta-emitting radioiodine deposited in the thyroid gland. Factors which influence the type and frequency of thyroid disease associated with radiation exposure include type of radiation, dose, dose rate, sex, current age, and age at exposure. Animal data and limited human studies indicate that at external radiation doses of 1500-2000 rad, cell killing and sterilization seem to predominate over carcinogenesis[24-28]. Therefore, estimates of risk for thyroid neoplasia are based on doses to the thyroid of less than 1500 rad of gamma radiation[24]. Doses higher than 1500 rad result in ablation of thyroid cells, thus predisposing to hypothyroidism.

7.3.3 Thyroid Neoplasms.

Thyroid cancer is a rare, indolent neoplasm with high five year survival rates (>80%) with nearly a three fold higher rate in women (incidence rates of 4 per 100,000) than men. However, prevalence of thyroid cancer at autopsy (not diagnosed while subject was alive) can be up to 28%. Over 90% of thyroid cancers are epithelial in origin, and the most common tumors are papillary carcinomas (40-70%, least malignant), follicular carcinoma (10-40%), and undifferentiated carcinoma (5-25%, highly malignant). Radiogenic thyroid cancers are mostly papillary carcinomas[29].

Apart from ionizing radiation (discussed below), the etiology of thyroid cancer is not well understood. Postulated risk factors include hormonal factors because of higher incidence in women, goiter, thyrotoxicosis, thyroiditis, genetic, ethnicity and/or unidentified environmental factors[29,30].

Thyroid Neoplasia-External Gamma Radiation. The two major sources which have

provided evidence linking ionizing radiation with the development of thyroid neoplasms in humans include 1) studies of persons who were previously exposed to gamma radiation in childhood for treatment of benign diseases of the head and neck, such as fungal infections of the scalp, cervical adenitis, acne, tonsilar hypertrophy, and suspected thymic enlargement[30-33]; and 2) studies of Japanese A-bomb survivors who were exposed primarily to external gamma radiation[34,35].

Follow-up studies of several cohorts exposed in childhood to external gamma radiation and evaluated for the subsequent development of thyroid neoplasia collectively demonstrate a dose-response relationship between gamma radiation dose and the development of benign thyroid adenomas and thyroid carcinomas[36]. Table 7-2 summarizes selected characteristics of six principal studies reported to date[37-42]. The range of mean doses evaluated has been between approximately 6 and 808 rad to the thyroid. Estimates of absolute excess risk per million person-year-rad (PYR) range from 0 to approximately 4, averaging about 2.5 per million PYR. Among people exposed in childhood to external gamma radiation, the absolute risk for total thyroid nodules has been reported to be 12.3 excess cases per million PYR (which includes thyroid cancer). Assessments of Japanese A-bomb survivors exposed primarily to gamma radiation show a similar dose-response relationship for thyroid carcinoma based on T65DR dosimetry[34]. Nagataki and colleagues[35] recently reported a study of thyroid disease in 2587 A-bomb survivors from Nagasaki using the revised DS86 dosimetry estimates for thyroid dose. They found a significant dose-response relationship for solid thyroid nodules (N=90 [75 females, 15 males]), which included cancer , adenoma, adenomatous goiter, and nodules without histological diagnosis. Although the association between thyroid dose (DS86) was not statistically significant with the prevalence of thyroid cancer (N=21 [18 females, 3 males) ($p=.08$), it was significant when the analysis was repeated using the old T65D dosimetry ($p<.01$). Women and those who were of young age at exposure had significantly higher prevalence rates.

Thyroid Neoplasia-Exposure to Internally Deposited Radioactive Iodine. Although animal studies clearly indicate that internally absorbed ^{131}I can induce thyroid cancer[24,43,44], relatively little information is available in relation to the induction of thyroid neoplasia in humans from internal doses of ^{131}I. Furthermore, after reviewing animal data and human studies, it has also been suggested that radiation doses from internally deposited ^{131}I may be one-third[28] to two-thirds as effective as external photon irradiation[24].

The principal sources of evidence from human populations include studies of 1) persons receiving therapeutic (high) doses of ^{131}I for Graves' disease or thyrotoxicosis and persons receiving diagnostic (lower) doses for suspected thyroid disease, and 2) populations exposed to radioiodine from radioactive fallout in the Marshall Islands and Southwestern Utah. In the former, there is no overall convincing evidence that the risk of thyroid cancer is increased among persons receiving therapeutic doses of ^{131}I[24,30,45,46].

Table 7-2 Summary of Cohort Studies of Thyroid Neoplasia in Relation to External Gamma Exposure (from Davis, HTDS Protocol)

Source	# Irradiated	Mean Thyroid Dose (Rads)	Dose Range (Rads)	Mean Period of Follow-up (Years)	Absolute Excess Risk Per 100,000 PY-Rad*
Ron, 1989	10,834	9	4.3-16.9	30.0	12.5
Hempelmann, 1975	2874	119	17-685	24.2	38
Maxon, 1980	1266	290	210-1130**	21.5	18
Shore, 1976	2215	6	4-8	20	0
Frohmann, 1977	1476	808	55-898+	28	26
DeGroot, 1983	416	451	0-1372	26.4	8.3 ++

* Person-Year Rad
** For those with thyroid cancer
\+ 55-809 for 85% of the cohort; 684-898 for 91% of the cohort
++ Based on average thyroid absorbed dose of 451 rads; reported as incidence of thyroid cancer among the 416 examined patients per 100,000 persons per rad per year

These negative findings may be partially explained by the fact that most persons studied were adults at the time of exposure (although results do not differ in those studies that have included children), that the periods of follow-up have been generally shorter than those of the cohorts exposed to external gamma radiation, that the radiation doses to the thyroid were high (generally 2,000 - 10,000 rad), and that all persons studied had existing thyroid disease prior to treatment with ^{131}I[23]. Similar results have also been reported among persons exposed to much lower doses (generally 50-100 rad) through diagnostic procedures[47,48].

Residents of southwestern Utah who had been exposed to ^{131}I from radioactive fallout from nuclear testing in the Nevada Test Site between 1951 and 1958 have also been studied. Although initial reports from surveys of the thyroid status of a cohort of 4818 school children in the exposed areas relative to a control area indicated no difference in the prevalence of thyroid abnormalities, subsequent reanalysis of these data by different authors suggested up to a 30% excess of all types of thyroid abnormalities among the exposed group[23]. Recently, Kerber and colleagues[18] re-examined this cohort to estimate their current thyroid status. They also were able to estimate individual radiation doses by combining food consumption data with radionuclide deposition rates provided by the U.S. Department of Energy and a survey of milk producers operational during the nuclear weapons testing period. Doses ranged from 0 mGy to 4600 mGy (0 to 460 rad), and averaged 170 mGy (17 rad) in Utah. Although limited by the small number of exposed individuals and low incidence of thyroid neoplasms, they found a statistically significant excess of thyroid neoplasms (benign and malignant; n=19), with an increase in excess relative risk of 0.7% per milligray. Malignant neoplasms, when considered alone, were not significantly elevated. Among subjects exposed to doses greater than 400 mGy (40 rad) (rate of thyroid nodules 18.6 per 1000 subjects), they also noted an adjusted relative risk of 3.4 for thyroid neoplasms compared to those exposed to 0-49 mGy (rate of thyroid nodules 3.2 per 1000 subjects), and a non-significant positive dose response slope for carcinomas and nodules.

Although limited by lack of precise dosimetry, studies of the Marshall Islanders, who were exposed to radioactive iodines from nuclear fallout during atmospheric testing, suggest that persons exposed to mixed radioactive iodines (including the high-energy emitters ^{132}I, ^{133}I, and ^{135}I with much shorter half-life than ^{131}I) are at a much higher risk for developing thyroid morbidity and that the prevalence of both benign and malignant thyroid nodules all increase with dose[30,49]. In contrast to exposure to ^{131}I alone, exposure to the higher energy radioactive iodines with shorter half-life appears to be nearly as effective as external gamma radiation in producing both benign and malignant thyroid neoplasms[30,49].

7.3.4 Hypothyroidism.

It is estimated that ionizing radiation at external doses above 1500 rad may cause enough damage to the thyroid to produce hypofunction of the gland and permanent hypothyroidism[24], although lower doses may produce partial hypothyroidism.

Similarly, in persons treated with ^{131}I for Graves' hyperthyroidism, 50 of such individuals

receiving 20,000-25,000 rad of ^{131}I became hypothyroid five years after exposure. A strong linear dose-response was demonstrated in these studies with the lowest doses in the 2,500 rad range. Data in this range indicate that approximately 15% of persons exposed would develop hypothyroidism within five years of exposure[36].

A study of Israeli children irradiated for tinea capitis has revealed higher absolute risk estimates (14 per million PYR) resulting from lower thyroid doses (average 9 rad; range 4.3-16.9 rad)[37]. A recent study of thyroid disease in 2587 Nagasaki A-bomb survivors (1586 of whom had DS86 dose estimates) found 78 who had clinical hypothyroidism; 13 subjects had postablative hypothyroidism and 43 had spontaneous hypothyroidism with 27 being antibody positive. This study also showed for the first time the presence of autoimmune hypothyroidism in A-bomb survivors and displayed a downward concave dose response relationship reaching a maximum (±SE) level of 0.7±0.2 Sv[35].

7.3.5 Parathyroid Disease: Hyperparathyroidism.

Hyperparathyroidism is a clinical condition associated with excess production of parathyroid hormones, which may be asymptomatic or manifest as kidney stones, bone pain/lesions, or symptoms of elevated calcium (memory loss, depression, proximal muscle weakness, and nausea).

Although the relationship between external gamma radiation in the development of hyperparathyroidism is reasonably well established, there is little evidence to support this relationship with radioactive iodine exposure[23]. Although animal studies have indicated that parathyroid hyperplasia or adenomas develop in rats given ^{131}I to a greater degree than in control animals[24,50], such evidence is lacking from human studies. While the mechanism of parathyroid tumor induction in individuals exposed to external radiation is almost certainly due to direct photon beam exposure, the mechanism of postulated parathyroid tumor induction from radioactive iodine is less certain. Although the parathyroid glands do not take up radioactive iodine, a plausible mechanism would be from exposure to beta radiation from ^{131}I, taken up in adjacent thyroid cells. Although the number of cases is quite small in a study by Bondeson and colleagues[51], the development of parathyroid adenomas near the site of thyroid remnants treated with ^{131}Isupports this hypothesis.

Since the first case report of hyperparathyroidism in an individual exposed to head and neck radiation by Rosen and colleagues in 1975[52], 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 and colleagues[53] reported that 14% (doses range 0.6 - 45.7 gray) of 444 persons who were previously treated with x-rays for tuberculous cervical adenitis subsequently developed hyperparathyroidism at least 24 years after treatment, compared to a rate of 1.3% in an age matched population. More recently, Cohen and colleagues[54] in a cohort of 2923 of 4297 patients who had received radiation to the tonsils of approximately 800 rad (8 gray) before the age of 16, found that the incidence of clinical hyperparathyroidism was 18.7 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[23]. 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 developing thyroid cancer if they 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. A recent study of hyperparathyroidism among atomic bomb survivors in Japan corroborate the above results[55]. The prevalence of hyperparathyroidism was found to be increased in individuals exposed to 1 gray (100 rad) 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.

In a recent retrospective report, Bondeson and colleagues[51] reported on 600 consecutive cases of primary hyperparathyroidism, ten of which had a documented history of prior ^{131}I treatment. Such treatment had been given for either Grave's Disease or for ablation of thyroid remnants. Age at the time of ^{131}I therapy ranged form 21 to 72 years with the detection interval of hypercalcemia being between 3 and 27 years. The above authors also indicate that parathyroid adenomas developed at the sites of thyroid remnants in cases with ^{131}I ablation after thyroid tumor operations.

7.3.6 Studies in Progress.

The Hanford Thyroid Disease Study (HTDS). The HTDS was mandated by an act of Congress in 1988, following which the Centers for Disease Control selected a team of investigators headed by Dr. Scott Davis from the Fred Hutchinson Cancer Research Center (FHCRC) and the University of Washington in Seattle to conduct the study. The primary objective of the study was to determine whether thyroid morbidity, including but not limited to hypothyroidism, and benign and malignant neoplasia, is increased among persons exposed to releases of radioactive iodine from the Hanford Nuclear Facility between 1944 and 1957 (estimated amount of releases 740,000 curies), and who received radiation doses to the thyroid as a result, compared 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 a dose-response relationship. The study has recently completed a pilot phase in which 91% of 1590 study subjects identified from birth certificates were located, and data collecting mechanisms validated. The full study which will collect data on an additional 1600 subjects is expected to be completed by mid 1997. A major strength of this study is the availability of individual estimates of thyroid doses using state of the art dosimetry. The study has been carefully designed to have adequate statistical power be able to address the issue of whether exposure to radioactive iodine increases the risk of thyroid disease[11]. Since this study could potentially serve as an excellent

model for evaluating thyroid disease associated with ^{131}I exposures in the Oak Ridge setting, an executive summary of the HTDS Pilot Study Report is attached as Appendix M for more information.

Chernobyl. In the 1986 Chernobyl nuclear reactor accident in the former Soviet Union, an estimated 100 million curies of radioactive materials, including an estimated 7 million curies of radioactive iodines, were released [56], exposing an estimated 1.5 million people, including 160,000 children under 7 years of age, in the general area. Although 70% of the contamination occurred in neighboring Belarus, large parts of the Ukraine and the Brynsk area of Russia were also affected [57]. Mean thyroid dose estimates to individuals range from 2-5 Gy (200-500 rad) in the most heavily contaminated areas and 1 Gy (100 rad) in the less heavily contaminated areas[58]. In the Gomel and Mogilov regions of Belarus, 300 km from Chernobyl, doses to the thyroid exceeded 10 Gy (1000 rad) in 1% of children [57].

Preliminary studies of the exposed population have reported an excess risk of thyroid cancer but not leukemias and other cancers[57-59]. In affected areas of all three countries, 600 cases of thyroid cancer to date have been reported, a 100-fold increase on the normal incidence of 0.5 cases per million per year[57]. Follow-up studies of adverse health outcomes in defined cohorts of this population are currently underway. The findings of these studies should provide a better understanding of the relationship between exposure to radioactive iodine and subsequent risk of thyroid disease.

8. Cesium-137 and Other Radionuclides

The dose reconstruction feasibility study[1] identified several other radionuclides, mostly products of nuclear fission, such as cesium-137, ruthenium-106, strontium-90, that were released off-site from the ORR. These radionuclides, with the exception of ruthenium-106 (half-life of 367 days) have long radioactive decay half-lives (half-lives of cesium-137 and strontium-90 are 30 and 28.1 years, respectively) and persist in the environment for many years. Individuals could be exposed to these contaminants via ingestion of contaminated food/water or via external sources. The exposures could have led to doses to a variety of organs and the "whole body" and such exposures may increase the risk of cancer and other health effects. In this section, we will briefly discuss the properties of cesium-137 as an illustration and also uranium and discuss the health effects associated with these radionuclides.

8.1 Cesium-137- Description.

Cesium is an alkali metal that has 21 radioactive isotopes, of which ^{137}Cs is the most common, and resembles potassium metabolically. Unlike potassium, Cs is not an essential trace element for humans. Like ^{131}I, ^{137}Cs is a by-product of nuclear fission and is one of the more significant fission products, with a radioactive decay half-life of approximately 30 years, and is primarily a beta emitter, although it also emits gamma ray during decay[22]. The main sources of ^{137}Cs are from radioactive fallout of atmospheric weapons testing, fuel of nuclear reactors (where some are released to the environment), and from fuel reprocessing plants where the ^{137}Cs is released mainly as liquid effluents[22]. It is also used in industry as a sealed gamma source for measuring thickness of materials, and in medicine, as a sealed source for radiotherapy and also as a tracer (Table 8-1).

In general, ^{137}Cs tends to get firmly fixed in soil and also in sediments. With its long half-life (30 years), it can pose an exposure risk to humans for many years. It transfers to plants directly or through minimal uptake from roots, and may also transfer to milk and meat. Human exposure can be through dietary uptake of grain products, meat and milk. Its concentration in freshwater is higher than saltwater fish. It tends to bioconcentrate in algae and water plants and plants (x 1000) but much less in fish (x 60)[22].

In humans, ^{137}Cs is readily absorbed from the gastrointestinal tract, and because of its solubility migrates rapidly into cells of the body and becomes relatively uniformly distributed throughout soft tissues of the body. Selective uptake in bone appears to be limited to the bone marrow. It is rapidly excreted via the kidneys with a biological half-life ranging from 68-165 days; infants and children having shorter biologic half-lives. It readily crosses the blood-brain and placental barriers. Dose from ^{137}Cs in tissue is primarily due to beta particles[22].

Uranium. The ORR has used uranium in the fuels of reactors at ORNL and also processed fuels from off-site reactors, especially for separation of desirable fission products. Uranium is a naturally occurring metal present in rocks, soil, water, plants and animals. Natural

uranium consists mainly of uranium-238 (99.27%), uranium-235 (0.72%), and uranium-234 (.0054%). Uranium-235, being more radioactive, is enriched (i.e., extracted or concentrated) from natural uranium for use in nuclear weapons or nuclear power reactors. Left over uranium can still be a radiation and a chemical hazard. Uranium-238 is unstable and breaks down ('decays') emitting radiation and decay products. It decays very slowly with a half-life of 4.5 billion years. Initially, as U-238 decays, it releases high-energy alpha particles. This is followed by two beta decays (producing thorium-234 and short lived protactinium-234, successively). Then there is additional alpha emissions from other progeny: uranium-234, thorium-230, radium-226, and radon-222 [60].

Absorption of natural uranium by the body depends on its physical state, chemical form, and route of exposure. If inhaled, it enters the body via the lungs and is excreted within a few days by the kidneys. If ingested, 99% is excreted in feces, with only 1% entering the blood. If inhaled, it is absorbed from the lungs into the blood circulation and excreted via the kidneys within a few days. Based on animal experiments, 20% of uranium in blood is retained with an effective biological half-life of 20 days, and 2.3% has an effective half-life of 5000 days. Most of it is deposited in the bones and some in the kidneys, remaining there for many years[60].

8.2 Characteristics of Releases from the ORR.

In Oak Ridge, ^{137}Cs together with other radionuclides were released to White Oak Creek to the Clinch River and the portion of the Tennessee River above the Watts Bar Dam from early 1944 through the early 1960s[1]. Although the magnitude of releases is unknown, existing data suggests the total is orders of magnitude less than the total ^{131}I releases. The primary pathways of human exposure are expected to be consumption of aquatic biota in the Clinch and Tennessee Rivers, use of contaminated water for drinking, direct exposure to shoreline sediments, and consumption of agricultural produce grown on soils contaminated through irrigation or dredging of sediment[61]. Because of its long half-life and adsorbing capacity to soil and river sediments, unlike ^{131}I, it is persistent in the environment and humans may potentially be exposed to it.

8.3 Natural and Man-made Sources of Radiation.

To put in perspective the risk of adverse health effects associated with man-made sources of ionizing radiation, it may be helpful to first look at the levels of natural background radiation. In the U.S., over 80% of background radiation is estimated to be from natural sources, and 15% from medical (x-ray, nuclear medicine) sources. Exposures from occupational, nuclear facilities and radioactive fallout currently account for less than 0.4%[24]. However, these values do not reflect past levels of exposure, which were probably significantly higher than the present. Table 8-2 lists the primary sources (natural and man-made) of radiation exposure in the U.S. Appendix N is a table describing the various units used in measuring radiation[62].

Table 8-1 Summary of Properties of ^{137}Cs and Characteristics of Releases from ORR

^{137}Cs	
Properties	
Origin	Fission product
Sources from:	Radioactive fallout from nuclear weapons testing Fuel from nuclear reactors Fuel reprocessing plants
Radiation emitted	Mainly beta rays; decay accompanied by moderate amounts of gamma rays
Radiation half-life	30 years
Route/pathway of exposure	Ingestion
Distribution in human body	Well absorbed, uniformly distributed soft-tissues of the body and also bone marrow
Excretion	Kidneys
Biological half-life	68-165 days
Crosses blood/brain and placental barriers	Yes
Use	Used in industry as a sealed gamma source for measuring thickness of materials In medicine, as sealed source for radiotherapy and as a tracer
Characteristics of Releases from the Oak Ridge Reservation	
Source/Type	Various chemical separation programs in X-10 (ORNL)/ mostly from liquid effluents
Years of releases	Late 1943-1960s
Amount	Unknown
Population at potential risk	Population exposed through water and fish along White Oak Creek, Clinch River, and portion of Tennessee River covered by Watts Barr Dam. External exposure is also a potentially important pathway.

Table 8-2 Average Amounts of Ionizing Radiation Received Annually from Different Sources by Members of the US Population[43].

Source of Radiation	Average Dose Equivalent to Soft Tissues (mSv)		Average Annual Effective Dose Equivalent	
	mSV	mrem	mSv	% of Total
Natural				
Radon*	24	2,400	2.0	55
Cosmic	0.27	27	0.27	8
Terrestrial	0.28	28	0.28	8
Internal	0.39	39	0.39	11
Total natural	---	---	3.0	82
Man-made				
Medical				
X-ray diagnosis	0.39	39	0.39	11
Nuclear medicine	0.14	14	0.14	4
Consumer products	0.10	10	0.10	3
Other				
Occupational	0.009	0.9	<0.01	<0.3
Nuclear fuel cycle	<0.01	<1.0	<0.01	<0.03
Fallout	<0.01	<1.0	<0.01	<0.03
Miscellaneous**	<0.01	<1.0	<0.01	<0.03
Total man-made	---	---	0.63	18
TOTAL	---	---	3.60	100

* Dose equivalent to bronchi from radon daughter products. The assumed weighting factor for the effective dose equivalent relative to whole-body exposure is 0.08.

** Department of Energy facilities, smelters, transportation, etc.

8.4 Health Outcomes of Primary Concern

8.4.1 Adverse Health Effects of Ionizing Radiation.

Ionizing radiation and its effect on human health has been extensively studied over the past few decades. Non-human sources of evidence have been obtained from basic cellular and animal studies in the laboratory. Much of the human data has been obtained from findings of studies of several cohorts defined by individuals who had been exposed to relatively high doses of radiation. These include 1) atomic bombings of Hiroshima and Nagasaki, 2) diagnostic and/therapeutic irradiation for medical conditions, 3) occupation (luminous dial painters, uranium miners, radiologists, nuclear workers), and 4) radioactive fallout from nuclear weapons testing[24,64].

Although the adverse health effects associated with exposure to high doses of ionizing radiation are well established, they are not as well documented for exposure to low or fractionated doses (the magnitude of exposure that might be expected to occur in the general population living near nuclear facilities). Thus, data from the higher dose studies have been extrapolated to estimate risk at the lower levels of exposure, especially with regards to its carcinogenic and genetic effects, where a no-threshold effect is assumed. However, the appropriateness of this is an ongoing controversy in the radiation health field[24,65].

Health outcomes associated with exposure to ionizing radiation are related to its carcinogenic, genetic, and/or teratogenic effects (i.e., from prenatal exposure)[24,65]. Ionizing radiation is presumably capable of inducing all forms of human cancer, with the exception of Hodgkins lymphoma and chronic lymphocytic leukemia. However, because of the differential radiosensitivity of various body tissues, carcinogenic effects vary by site. The more common radiogenic cancers are leukemia, non-Hodgkin lymphoma, multiple myeloma, lung cancer, thyroid cancer, brain/nervous system tumors, breast cancer, ovarian cancer, liver cancer, malignant melanoma, and bone cancers. Apart from molecular changes, parental exposure to ionizing radiation prior to conception may result in genetic (i.e., heritable) changes which may manifest in increased cancer risk or in congenital anomalies[24,65]. When the developing embryo or fetus is exposed to ionizing radiation *in utero*, teratogenic effects can occur, which may manifest as adverse pregnancy outcomes (stillbirths, spontaneous abortions), congenital anomalies, mental retardation, and molecular changes[24,66]. However, all of these effects have not been consistently demonstrated in studies of human populations. In evaluating these outcomes, factors to consider include type, dose, duration of radiation, sex, age at exposure, and health status of the exposed individual, and other confounding factors associated with the specific conditions. Furthermore, radiation induced health effects do not have characteristics to distinguish them from similar conditions from other causes. For example, radiation-linked leukemias are no different than those thought to be caused by other etiologic agents[65,67]. However, with advances in molecular research, it may be possible to identify molecular fingerprints in the DNA sequences of cancer cells unique to radiation injury. For example, investigators looked for and found activated *ret* oncogene by rearrangement (translocation) in four of seven cases of childhood thyroid cancer in Chernobyl since these changes are believed to be specific to radiation. However, of

nineteen cases in this series, they were able to study only seven where they were successful in isolating RNA particles[68]. The *Committee on the Biological Effects of Ionizing Radiations-BEIR V Report*[24] and the *UNSCEAR Sources, Effects and Risks of Ionizing Radiation Report*[69] have extensively reviewed the health effects of low levels of ionizing radiation.

The following sections will briefly describe radiation-linked cancers (except for thyroid cancer which is discussed in section 7), teratogenic and carcinogenic effects associated with *in utero* exposure to ionizing radiation, genetic effects associated with parental preconception exposure to ionizing radiation, and studies of populations who may have been exposed to low levels of radiation from living near nuclear facilities with emphasis on population studies in the Oak Ridge area.

8.4.2 Radiation-linked Cancers.

Leukemia. The leukemias encompass a diverse group of malignancies that arise from cell systems that circulate in peripheral blood and that arise in large part from the bone marrow[70]. They account for roughly 5% of the total annual cancer incidence in the U.S., and constitute nearly one-third of all childhood cancers. The leukemias are characterized by temporal course as chronic or acute, and by the nature of the leukemic cells. Based on the types of cells, four main types of leukemia include acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML), chronic myelocytic leukemia (CML), and chronic lymphocytic leukemia (CLL). Incidence rates by age, gender and race vary considerably by type of leukemia. Acute leukemias are common in all ages and account for almost all leukemias in children and young adults and for about two-fifths of those in older adults. CLL is rarely seen before adulthood but is common over age 50. The incidence of leukemia is higher in males and in whites[70].

The etiology of leukemia is slowly being understood. Chemotherapy for other cancers and ionizing radiation are well established causes of leukemia. Benzene has been shown to cause AML in humans and other organic chemicals, gasoline, pesticides are suspected leukemogens. A viral component to leukemia etiology also has been suggested but remains to be confirmed[70-72]. It is also associated with some genetic syndromes, such as Down's syndrome and Fanconi's anemia. Role of parental exposure to mutagenic substances with subsequent increased risk of developing childhood leukemia has lately aroused some controversy[66].

The induction of leukemia by ionizing radiation has been well documented in humans and laboratory animals[24]. Leukemia was the first cancer reported in excess among A-bomb survivors.[70] All major forms of leukemia, except CLL, have been shown to be increased in human populations following exposure to ionizing radiation. Leukemias are estimated to account for 20% of excess deaths in the A-bomb survivors cohort[73]. The most recent analyses of incidence of leukemias in the A-bomb survivors cohort (93,696 survivors with 2,778,0000 person years of follow-up from 1950-1987) by Preston and colleagues found a statistically significant dose response for all three subtypes (ALL, AML, and CML), that appears to non-linear. The excess leukemias peaked within 10 years, and those exposed to higher doses (>3-4 Gy) were not included in the analyses, because the bone marrow cells would probably have been killed at the

high doses. The authors estimated excess absolute risks of 0.6, 1.1, and 0.9 cases per 10,000 person years per sievert for ALL, AML, and CML, respectively with corresponding excess relative risks per sievert of 9.1, 3.3, and 6.2[73].

ALL in young children is considered to be the most sensitive marker for exposure to radiation[70,74]. Young age at exposure and males are at increased risk. However, at lower levels of exposures, although the trend is suggestive of increased risk for leukemia[19], the evidence from epidemiologic studies, especially those of populations living near nuclear facilities, is inconclusive, primarily because of the limitations of these studies.

Non-Hodgkin's Lymphoma and Multiple Myeloma. Lymphomas are cancers of the lymphorecticular system, and characterized by the abnormal growth of lymphocytes in the lymph nodes, spleen, and thymus. Lymphoid cells in other organs such as tonsils, stomach, small intestine, and brain may also be affected. Hodgkin's disease is the most common specific type of lymphoma. Rarer lymphoreticular cancers of distinct origin include Burkitt's lymphoma and plasma cell neoplasms. The remaining lymphoreticular cancers comprise a heterogenous assortment of different lymphoid cell neoplasms and generally are referred to as non-Hodgkin's lymphoma[75].

The non-Hodgkin's lymphomas are among the less common cancers in the U.S., accounting for 2% of all cancers. Incidence generally increases with age and is higher in males than females. Etiology is not well understood. Immunogenetic factors apparently are important, as illustrated by lymphoma prone families and the greatly increased risks following therapeutic immunosuppression. Some medications have been suspected (e.g. phenytoin) to play an etiologic role. The role of environmental risk factors is unclear. A positive gradient with socioeconomic status and urbanization has been observed in mortality studies. Occupational studies involving various chemical exposures have been inconclusive.

Although ionizing radiation can induce lymphomas in various animal species, the evidence is less clear in humans. Although excess mortality has been observed in persons receiving therapeutic irradiation for ankylosing spondylitis, it has not been seen in A-bomb survivors[24]. Preston and colleagues[73] did not find an excess risk of non-Hodgkin's lymphoma in the most recent analyses of incidence data on the A-bomb survivor cohort, although there appeared to be an excess among males. Several other irradiated groups have not shown an excess of NHL[24,75].

Multiple myeloma is a malignant proliferative disorder of B-cell lineage and is considered to originate in differentiated B-lymphocytes. Animal studies have supported and epidemiologic studies of populations with low, protracted exposure to ionizing radiation have suggested an increased risk, which was supported by initial studies from the A-bomb survivors, which reported a statistically increase in risk[24]. However, the most recent analyses of this cohort which included additional years of follow-up and more cases did not find an excess risk[73]. Further data in humans is needed for low doses characteristic of occupational and environmental exposures.

Melanoma of skin. Melanoma is a cancer of the melanocyte, the skin cells that produce

the dark pigment melanin. Melanomas can occur almost anywhere on the body, but in light-skinned persons they occur most often on the trunk in men and on the lower legs in women. The head, neck, and arms are other common sites. In dark-skinned people, melanomas occur most often on the palms of the hands and soles of the feet. Melanoma incidence in the U.S. is roughly ten times higher in whites than in blacks.

The etiology of melanoma remains uncertain. Melanoma is related to exposure to the ultraviolet (UV) component of solar radiation, but not in a clear manner. Since melanomas may occur on sun-shielded areas of the body, other etiologic factors likely exist. Family studies suggest that some melanomas result from inherited susceptibility traits. The role of environmental factors other than solar UV is uncertain, although there have been case reports associated with PCB exposures[76]. Evidence showing an increase in melanoma among human populations exposed to ionizing radiation has not been consistent[24,75].

Lung Cancer. Lung cancer accounts for 15% of all cancer in U.S. adults (22% in males and 8% in females) and due to its poor prognosis, 25% of all cancer deaths (34% in males and 15% in females). The incidence of lung cancer in the U.S. (1983-87) was 62.5 per 100,000 population in males and 29.9 per 100,000 in females, and increases with age, with higher rates after age 60. Although both genders have experienced an increase in lung cancer rates over the past four decades, the increase has been disproportionately in females, with a five fold increase in rates during this period. This increase has largely been explained by the increasing prevalence of smoking among women during the same time [77,78].

Histologically, lung cancers mainly arise from epithelial tissues. The three most common types include squamous cell carcinoma, adenocarcinoma, and small cell anaplastic carcinoma. Squamous cell carcinoma accounts for nearly 35% of all lung cancers, is found more in males and is closely related to smoking. Adenocarcinoma accounts for nearly 35% and is common in females and less closely related to smoking. Small cell anaplastic carcinoma is more common in males and closely related to smoking [77,78].

In addition to smoking, other risk factors associated with lung cancer include gender, religion, ethnicity, age, radiation, and exposure to occupational and environmental respiratory carcinogens, including polycyclic aromatic hydrocarbons, arsenic, asbestos, chromium, nickel, radon progeny, and chloromethyl ethers. However, smoking is the predominant risk factor, accounting for an estimated 80% of lung cancers in males and 40% in females in the U.S. [77,78].

Studies of individuals irradiated therapeutically for ankylosing spondylitis, uranium mine workers exposed to radon and its daughter products, and the A-bomb survivors in Nagasaki and Hiroshima have shown significant excesses of lung cancer associated with exposure to ionizing radiation. Using DS86 exposure data, the relative risk of lung cancer mortality at 100 rads was 1.63 (90% confidence interval 1.35-1.97) and the absolute risk was 1.68 excess lung cancer deaths per 10^6 person years (90% confidence interval 0.97-2.49) in the Japanese A-bomb survivors [24]. Whether smoking has an additive or a multiplicative effect on the risk of lung cancer associated with radiation exposure is not clear. However, smokers appear to have higher relative risks of lung cancer associated with different levels of exposure than non-smokers.

Studies of uranium miners in the U.S., Canada, and central Europe have shown an increased risk of lung cancer with exposure to radon and its daughter products. The risk of lung cancer in those with the highest exposures (>3,700 working level months) after adjusting for smoking was 20 fold higher[77].

Liver and Intra-Hepatic Bile Duct Cancer. Primary liver cancer is uncommon in the U.S., accounting for roughly 0.5% of all cancers diagnosed annually. Liver cancers are divided into epithelial and nonepithelial neoplasms. Epithelial cancers predominate, of which hepatocellular carcinoma and cholangio-(intra-hepatic bile duct) carcinoma respectively constitute approximately 70% and 20% of all primary liver cancers. Non epithelial liver cancers are exceedingly rare, but have been extensively studied because of their association with certain chemical and radiochemical exposures. Except for a small peak in young children, the incidence of liver cancer generally increases with age. Incidence is typically higher in males than females[67].

The etiology of liver cancer is partially understood. A large percentage of liver cancer occurs in association with cirrhosis. Etiology factors include alcohol, hepatitis B virus, and aflatoxin. Vinyl chloride is known to cause hepatic angiosarcoma, a rare non-epithelial liver cancer. Thorotrast, an alpha-emitting contrast agent used between 1930 and 1955, is known to cause both epithelial and non-epithelial liver cancers[24]. Although liver cancer has not been observed in A-bomb survivors in past studies, the most recent analyses of liver cancer in the A-bomb survivor cohort (N=79,792) showed a dose response with excess relative risk for 1 sievert of 0.49 (95% CI, 0.16-0.92), the excess absolute risk of 1.6 cases per 10,000 person-year sievert (95% CI, 0.54-2.9), and an attributable risk percent of 10.9% (95% CI, 3.6-19.4[79].

Brain and Nervous System Cancer. The nervous system is made up of the central nervous system (which includes the brain and spinal cord) and the peripheral nervous system. Cancers of the nervous system are of many different types and are classified according to tumor cell type and location. The majority of nervous system cancers occur as brain cancers, of which the gliomas, including glioblastomas and astrocytomas, are common. Medulloblastoma, a brain cancer seen rarely in adults accounts for roughly one-quarter of all childhood brain cancers. Males typically have a higher incidence of brain cancer than females. Brain cancers rarely metastasize outside the central nervous system; however, the brain is a frequent metastatic site for tumors originating elsewhere in the body.

Although the etiology of brain cancer is poorly understood, studies have linked them with occupational, environmental, viral, and genetic factors, with differing etiologies among the different types of brain cancer. High- dose ionizing radiation given as diagnostic or therapeutic radiation to the head and neck in childhood has been shown to increase the incidence of nervous system tumors[7,24]. These tumors include malignant as well as benign growths of the brain, meninges, and peripheral nerves.

High doses of radiation in monkeys have demonstrated an increased incidence of glioblastoma multiforme and other types of intracranial tumors. Brain tumors have also been observed in rats and dogs following irradiation between 1-2 gray[24].

Evidence of excess mortality due to nervous system tumors was first seen in children exposed to diagnostic x-rays *in utero*[80], but the dose received was not clear. Although this excess was not seen in children exposed in utero of atom bomb survivors[81], the results were considered statistically not inconsistent with the previous studies. Several cohorts of patients who received therapeutic irradiation for medical conditions (tinea capitis, ankylosing spondylitis) showed an excess of nervous tumors[24]. Recently, Ron and colleagues[7] found a clear excess of brain and nervous system tumors (malignant and benign gliomas, meningiomas, nerve-sheath tumors, and other neural tumors) in a cohort of 10,834 patients who had been irradiated during childhood for tinea capitis (a fungal infection of the scalp) between 1948-1960 in Israel. Doses of radiation to the neural tissue were retrospectively estimated from information in the records on therapeutic dose, treatment, techniques, number of courses of therapy, and simulation studies performed using a simulated model of a 6 year old child (mean dose 1.5 gray). There was a nearly 7 fold increase in estimated risk in the irradiated subjects compared to 10, 834 matched general population controls and 5,392 siblings who had not been irradiated. A strong dose-response relation was found with the relative risk increasing from 7.2 at estimated doses of 1-1.3 gray to 20 at doses above 2.0 gray (see Figure 3-2).

Breast Cancer. Cancer of the breast is the second most frequently diagnosed malignancy, with age adjusted incidence rates of 85 per 100,000 women. Breast cancer is extremely rare before menarche. The rate goes up after age 30, with median age of 61 years at diagnosis. White women are at slightly higher risk than non-white. The major risk factors for breast cancer include a) demographic characteristics: age (increased rates after age 40), race (decreased rates in Asian women), and socioeconomic status (increased rates with high SES); b) genetic (positive family history: increased risk if first degree relative); c) reproductive: increased with early menarche, single marital status (increased after age 50), age at first pregnancy (increased over age 30), and oophorectomy (decreased if before age 40); d) pre-existing breast disease (increased if proliferative); e) ionizing radiation (increased if excess exposure in adolescence); and f) nutrition (increased with high fat, high protein diet).

Animal data have shown the sensitivity of breast tissue to radiation. Human breast tissue is considered to be highly sensitive to the adverse effects of ionizing radiation.[24] Indeed, this has led to some concern that the wide use of screening mammography might lead to excess risk of breast cancer if such screening were applied to women at otherwise low risk. An excess risk of breast cancer (risk ranging from 5.5 to 10.7 cases per 10^4 woman-years per gray) has been consistently reported for radiation exposure from different populations: the A-bomb survivors and past therapeutic radiation for various medical conditions, such as tinea capitis of the scalp, repeated chest fluoroscopy for tuberculosis, enlarged thymus, and ankylosing spondylitis[24,82,83]. This has been confirmed by the most recent analyses of breast cancer in the A-bomb survivor cohort (N=79,792) which showed a dose response with excess relative risk for 1 sievert of 1.6 (95% CI, 1.1-2.2), the excess absolute risk of 6.7 cases per 10,000 person-year sievert (95% CI, 4.9-8.7), and an attributable risk percent of 31.9% (95% CI, 23.2-41.1)[79]. The effect of radiation is greatly dependent on age at exposure, with low relative risk for exposure after age 40 years and

highest for exposure before age 20 years. However, the breast cancers do not appear before the age when they start occurring in the general population, lending credence to the role of hormonal factors[24,83]. There are little data to evaluate the risk of breast cancer from low doses of radiation, such as those commonly used in medical diagnostic procedures (mammography, chest radiography).

Ovarian Cancer. Ovarian cancer is the sixth most common malignancy in women in the US (incidence rates range from 11.5-15.3 per 100,000 women), accounting for 4% of all new cases and 27% of the reproductive system cancer. It accounts for 57% of deaths due to gynecologic cancers and fourth most common cause of death in women[84-86]. Epithelial tumors account for 90% of malignant tumors in the ovary. The etiology of ovarian cancer is poorly understood. Identified risk factors include family history of gynecologic cancer and cystic ovaries, nulliparity or low gravidity, difficulty in conceiving and infertility, and lack of use of oral contraceptives. Speculated risk factors also include exposure to infertility drugs, exposure to talc and asbestos[84-86].

Animal data clearly support the development of ovarian tumors following exposure to ionizing radiation. Although some studies of women exposed to therapeutic pelvic irradiation did not find an excess of ovarian tumors, follow-up studies of the A-bomb survivor show a relative risk of 2.33 per gray, especially among those exposed before age 20 years[24,87].
This has been confirmed by the most recent analyses of ovarian cancer in the A-bomb survivor cohort (N=79,792) which showed a dose response with excess relative risk for 1 sievert of 0.99 (95% CI, 0.12-2.3), the excess absolute risk of 1.1 cases per 10,000 person-year sievert (95% CI, 0.15-2.3), and an attributable risk percent of 17.7% (95% CI, 2.4-37.3)[79]. However, pertinent low-dose data for this carcinoma are even more limited than that for breast cancer.

Bone Cancers. Bone cancers are uncommon malignancies arising from the bone and cartilage and comprise less than 0.5% of all malignant neoplasms, an incidence rate of <1 per 100,000 persons, occurring more frequently in whites and in males. Based on cell of origin, the common types are osteogenic sarcoma, chondrosarcoma, fibrosarcoma, and Ewing's sarcoma. Their five year survival rates range from 15% for Ewing's sarcoma to 60% for chondrosarcoma[88].

The etiology of bone cancers is poorly understood, except for its link with exposure to high levels of radiation. Other etiological factors thought to be linked include chemical exposures, especially vinyl chloride, viruses, and possibly trauma[88]. Host factors that seem to predispose to cancer development include Paget's disease, other pre-existing bone defects, multiple myeloma, and family history.

Studies of cohorts receiving large doses of radiation can produce cancer, although dosimetry information is inadequate to establish dose-response associations. A-bomb survivor studies have not shown an excess of bone cancer resulting from levels of exposure in the 0-4 Gy range[24].

8.4.3 *In Utero* Exposure to Ionizing Radiation: Teratogenic and Carcinogenic Effects.

There is sufficient evidence to indicate that direct exposure of the highly radiosensitive rapidly developing embryo and fetus can result in teratogenic and also carcinogenic (i.e., increased risk of subsequent cancer) effects, especially if exposure occurs at critical stages of development[24,65,66]. Animal studies have demonstrated the development of malformations associated with exposure during critical stages of organogenesis with doses as low as 50 mGy[65].

Neurogenic Teratogenesis. Human studies of teratogenesis have been largely limited to the cohort of children (N=1630) born to A-bomb survivors who were exposed *in utero* to ionizing radiation. Microcephaly, defined as head circumference 2 or more standard deviations below the age- and sex-specific mean, is a well established teratogenic effect found in these children[89]. In addition, increased frequency of mental retardation, and reduced IQ at age 10-11, and seizures were seen in those children who were exposed during weeks 8-15 of gestation. Although a significant linear dose-response effect was seen, whether there was a no-effect threshold was unclear. No excess fetal and infant mortality and other congenital anomalies were seen. However, limitations of this cohort include the underascertainment of early reproductive wastage, high exposure doses, and the role of maternal radiation sickness on outcome[66,89].

Childhood Cancer. Although childhood cancers are rare, they nevertheless account for 11.3% of all deaths in childhood, second only to deaths due to injuries[90]. Because of significant progress in treatment, the cancer mortality rate in children 0-14 years of age dropped by 36% between 1973 and 1986, from 5.4 per 100,000 to 3.5 per 100,000. The most frequent childhood malignancies are leukemia, brain cancer, and lymphomas, which account for 62% of childhood cancers in the U.S.[90].

Despite the advances in treatment, the etiologies of most cancers in children remain enigmatic. Established risk factors include genetic disorders [91], therapeutic irradiation[38,92,93], and *in utero* exposure to diethylstilbestrol[94]. Maternal and infant characteristics that may be associated with increased risk of cancer include high socioeconomic status, increased maternal age, heavy birthweight[90]. Factors that are yet controversial include viral infections (pre- and post-natal), parental occupation, diagnostic irradiation, electromagnetic fields, and a variety of chemical exposures[90]. Although the epidemiology varies by cancer type, no clear differences in etiology have been established to date.

Stewart and colleagues first showed an increase risk of cancer for children who were exposed to diagnostic x-rays while *in utero*[66]. Except for a few smaller studies, the larger studies and bulk of evidence suggests that this association exists[95]. However, others have postulated that some characteristics of the mother, child, or the pregnancy may have both increased the cancer risk and also the frequency of prenatal exposures. Consistent with the findings of an earlier study of prenatal exposure and twins by Mole[95], Harvey and colleagues[96] found that twins with leukemia or childhood cancer were twice as likely to have been exposed to x-rays in utero as twins who were free of disease (relative risk, 2.4; 95% confidence interval, 1.0-5.9) in a case-control study based on data from 32,000 twins identified by linking Connecticut birth certificates and the Connecticut cancer registry from 1930 to 1969. Twins were studied to reduce the likelihood of

medical selection bias, since twins were often exposed to x-rays to diagnose the twin pregnancy or to determine fetal positioning before delivery and not because of medical conditions that may conceivably predispose to cancer.

However, Jablon and colleagues[81] in a study of 1292 Japanese children exposed prenatally to the atomic bombings in Japan did not find an excess risk of mortality due to leukemia or other cancers. Although a recent analysis of this cohort 40 years later did not show an increased risk of cancer, a dose dependent increase in cancer risk was seen[89]. Subjects exposed *in utero* to maternal uterine doses of ≥0.01 Gy had a two-fold increase in risk compared to those who were unexposed (0 Gy) (13 cases/920 exposed = 45.6/100,000 vs 5/710 = 22.4/100,000 unexposed)[89]. However, the number of cancer cases was too small to draw firm conclusions.

8.4.4 Genetic (Heritable) Effects-Preconception Radiation Exposure.

Genetic alterations in germ cells following maternal or paternal preconception exposure to ionizing radiation can be transmitted to the off-spring, in whom it may manifest as congenital anomalies or cancer[24,65,66]. Animal studies have shown that heritable mutations and chromosomal abnormalities can occur following exposure to preconception radiation to germ cells and that the frequency of these abnormalities increases with dose[24,65]. However, these effects have not been well established in humans.

Although studies of Down syndrome and maternal (but not paternal) preconception exposure to x-rays have been generally inconsistent but suggestive, Sever concluded that there is a possibility of increased risk of Down syndrome and other chromosomal abnormalities at preconception levels to which nuclear workers may be exposed[66]. However, the cohort of 72,216 children born to A-bomb survivors after May 1946 (i.e., conceived after the bombings) have not shown an excess of heritable effects, as measured by adverse pregnancy outcomes (major congenital anomalies, still births, birthweight, neonatal deaths, cancers, and other changes in chromosomal arrangements (including Down syndrome), and also in disturbances in normal growth and development[65,66,89].

Sever[97] and colleagues in a case control study of congenital malformations and occupational exposure to low levels of ionizing radiation in Hanford found increased risk of neural tube defects in children whose parents were occupationally exposed to radiation at the Hanford nuclear facility, but not for other malformations, including Downs syndrome. Partly because of the large number of statistical comparisons made and the negative findings from the A-bomb studies, the authors initially dismissed this finding[97], but in view of the Gardner findings (see below), they have partly revised their original conclusions[66].

A case-control study by Gardner and colleagues in the United Kingdom that found an increased risk of childhood leukemia associated with paternal occupational exposure to ionizing radiation prior to conception raised considerable interest and controversy regarding the heritable effects of radiation[8]. However, Gardner's hypothesis that preconceptional irradiation of the testis caused some mutagenesis resulting in an increased risk of leukemia in the offspring has been found to be invalid[98]. Reasons for refuting this hypothesis include the fact that it is inconsistent

with current knowledge of radiation genetics or of the hereditability of leukemia; it has not been observed in children of the A-bomb cohort, near the vicinity of nuclear facilities in Ontario, in Scotland, or in Cumbria other than Seascale[98]. The association that Gardner found is largely or wholly a chance finding[98]. A viral etiology has been offered as a potential explanation for the excess cases of leukemia in this region[99]. Nevertheless, there is an ongoing U.S. study to independently evaluate this hypothesis (see section 8.3.7).

8.4.5 Studies of Population Living Near Nuclear Facilities.

Because of ongoing concerns of whether populations living near nuclear facilities are at increased risk of adverse health outcomes due to exposure to low levels of ionizing radiation, and if so, what the magnitude of these risks are, many ecologic studies have been conducted in the United States[100-104], United Kingdom[100,105-109], Canada and Europe evaluating this issue[100]. Although some studies indicate an increased rate of disease, no study has convincingly been able to demonstrate a link between the increased risk and radiation exposure[100]. Several leukemia clusters in children have been reported in populations living near some facilities in the United Kingdom[106-108,110], prompting further studies, which led to, among others, the Gardner study discussed in the previous section. However, several possible explanations, including methodologic limitations, environmental factors other than radiation, viral, social factors and chance clusters have been offered for these findings. Cook-Mozaffari and colleagues[111]found excess mortality due to leukemia and Hodgkin's disease in children who lived near potential sites of nuclear facilities to be similar to existing facilities, postulating that areas near potential and existing sites may share common, unrecognized risk factors. Kinlen[112] found an excess mortality due to leukemias in children living in a new township built in a rural area, suggesting that rapid urbanization of a rural area which may be deficient in herd immunity to viruses may be the reason. Studies of populations living in US facilities have not found similar results[100,101].

In a comprehensive review, Shleien and colleagues[100] found that, in addition to limitations of ecologic studies, lack of adequate exposure information (exposure usually defined as living near vicinity of these facilities) with resultant misclassification of subjects and inability to show a dose response and general disregard for statistical power made the findings of these studies inconclusive.

Studies in the Population Living Near the ORR. To date, there have been five published ecologic studies[101-104,113] (Table 8-5) which have evaluated the health risk (mainly of cancer) of the off-site population living near the vicinity of the ORR. None of these studies except one showed an excess of cancer in this population. It is difficult to compare these studies because of differences in time periods and population studied and in analytic strategies used. These studies are limited by the problems inherent in ecologic studies ('ecologic fallacy', migration patterns, temporal ambiguity between exposure and development of disease, completeness of ascertainment

of cases, and also by their reliance on mortality data with its own limitations (see Section 3). Thus, because of these limitations, it is not possible to draw any firm conclusions from these studies whether the population living near the vicinity of ORR have significantly higher death rates from cancer than expected in other populations.

Moshman and Holland (1949)[102] compared the rates of cancer incidence of approximately 300,000 Oak Ridge residents (workers and off-site population) between 1943-1948 with estimated national rates based on cancer data from large US metropolitan areas. In comparison to the national rate of 230 cancers per 100,000 population, he calculated an age-adjusted rate of 123 (N=196) per 100,000 population in Oak Ridge. He found that white males had a higher proportion of cancers of the respiratory system. He attributed the low cancer rates to the 'healthy worker' effect. However, the major limitation of this study is the short time between possible exposure and the evaluation of cancer in the exposed. Nevertheless, this was the first study prompted by the possible carcinogenic effects of working and/or living near a nuclear facility.

Patrick (1977)[103]calculated rates of mortality for cancer, fetal deaths, infant mortality, and deaths from severe congenital malformation from mortality data for residents of Roane and Anderson counties for 1929-1971 and for the city of Oak Ridge for 1949-1971. He compared these rates with rates for residents of the rest of Tennessee state. Although there was no formal statistical testing, there was a slightly increasing trend, evident prior to the 1940s, in rates of cancer mortality in the study counties which paralleled the trend for the rest of Tennessee. No excess deaths were seen by age, sex, or race. Although based on only two cases, there was an excess of leukemia and lung cancer in non-white female residents of Anderson county. As acknowledged by the author, the limitations of the study include those inherent in ecologic designs, and quality of data (discussed in section 6).

Goldsmith (1989)[104] in a letter to the editor ascertained leukemia deaths observed in white children 0-9 years of age who were residents of Anderson and Loudon counties between 1950-1979 and computed expected deaths based on the US national rates. He found a statistically significant, excess number of deaths due to leukemia in residents of Anderson and Loudon counties for 1950-1959 (Table 8-3). However, the excess may be due to an underestimation of the population size in 1950-1959, not adequately reflected by linear extrapolation of the 1950 and 1960 census because of significant population movements[114] in these counties. It is not clear why Roane county was not chosen in the analysis. The author acknowledges the preliminary nature of the analysis and its limitations.

Table 8-3 Leukemia Mortality Before 1970 in Anderson and Loudon Counties

County	1950-1959		1960-1969		1970-1979	
	O	E	O	E	O	E
Anderson	13	6.65	8	5.16	2	2.57
Loudon	3	2.28	3	1.76	1	1.05
Both	16	8.93*	11	6.92	3	3.62

* $p < .05$ O = Observed E = Expected

Jablon et al (1991)[101] This study, the largest of its kind to date, conducted by the National Cancer Institute compared cancer mortality rates in people living in 107 U.S. counties (1980 population: 18.7 million) with or near 62 nuclear facilities and compared them to people in 292 matching counties (1980 population: 33 million) without nuclear facilities. The study looked at cancer deaths (all cancers and 16 specific types of cancer) from 1950 to 1984. During the study period, there were 37,200 leukemias and 838,000 other cancers in the study counties compared to 78,500 leukemias and 1,794,000 other cancers in the control counties. Although the study found that some of the study counties had higher rates of certain cancers, and some had lower rates, the authors' overall conclusion was that there was no evidence to suggest an increased risk of death from any of the cancers surveyed due to living near nuclear facilities.

In the Oak Ridge site, the study population included residents of Anderson and Roane counties. There were six control counties, which were selected from the same region and matched on several characteristics (proportion of population in 1979 over age 25 that are white, black, Hispanic, urban, rural, employed in manufacturing, and high school graduates; mean family income; net migration rate; infant death rate; population in 1979) in an attempt to ensure their comparability. Since these criteria were based on 1979 county characteristics, they could have changed significantly over the course of the study period, possibly making the comparability of the study and control counties questionable.

In the Oak Ridge site, the findings indicated that in the study counties there were a few excess cases of leukemia among children less than 10 years of age. In the control counties, there were fewer cases than expected. When the counties were compared, there was an increased rate in the study counties, but the increase was not statistically significant. For all age groups of leukemia, the rates were not significantly different between study and control counties. The study counties had significantly higher rates of all other cancer deaths (6% increase) (excluding leukemia) and of deaths due to cancer of the respiratory system (trachea, bronchus, and lungs) compared to control counties, although the SMRs were not increased (Table 8-4). The authors concluded that this was not likely due to the presence of nuclear facilities. Other important factors which were not

Table 8-4 Cancer Mortality in Anderson and Roane and Six Control Counties, 1950-1984

Cancer	Study Counties		Control Counties		RR
	O	SMR	O	SMR	
Age at Death: <10 Years					
Leukemias	33	1.34	49	0.91	1.47
Other cancers	24	0.90	50	0.84	1.07
Age at Death: All Ages					
Leukemias	230	1.02	598	0.99	1.03
Other cancers	4460	0.93	11657	0.88	1.06 *
Respiratory	1096	1.08	2408	0.87	1.24 *
Breast	391	0.84	964	0.78	1.08
Thyroid	13	0.86	43	1.08	0.84
Brain/nervous system	132	0.96	397	1.14	0.84

O = Observed, SMR = Standardized mortality ratio, RR = Relative risk * $p<.01$

measured, such as life style factors, household exposure to radon, smoking and tobacco use, and also the appropriateness of the control counties could explain the findings.

The authors have carefully described and acknowledged the study limitations, including reliance on mortality data, migration patterns, possible changes in comparability of population of study and control counties, and other inherent limitations of ecologic studies.

Mangano (1994)[113] In a recent study that has aroused considerable interest, Mangano calculated the rate of change in overall age and sex adjusted cancer mortality rates from 1950-1952 and 1987-1989 in a population which included 94 surrounding counties within 100 miles of Oak Ridge. He tested five hypotheses: 1) that there would be an increased change in the overall cancer mortality rates in the 94 study counties combined compared to change in similar US and Southeast Region rates for the same time periods, 2) that there would be an increased change in mortality rates in rural counties versus the urban ones within the 94 counties, 3) that there would be an increased change in rates in counties closest in proximity (within 40 miles) to the ORR, 4) that there would be an increased change in rates in mountainous counties because of increased precipitation compared to low-lying ones, and 5) that there would be an increased risk in counties that were downwind to the ORR. The author found statistically significant findings supporting all five hypotheses.

The major limitation of this study is its use of an ecologic design for hypotheses testing and establishing causal relationships, especially in diseases with multiple etiological factors and long latency, such as cancer. The ecologic study is a poor design for this purpose, as discussed in Section 3. The methods are not clear: for example, why a 100 mile radius was chosen to select study counties, what criteria were used to define rural and urban counties, mountainous and low lying counties (Was the precipitation in the mountainous counties actually higher than the low lying ones? If so, were the main population concentrations in low lying areas of mountainous counties or vice versa?). The downwind hypothesis assumes that possible radioactive emissions were released into the atmosphere, and ignores the role of other exposure pathways, such as food, milk, and the water, which are independent of wind directions. Only two brief time periods were used to compare change in rates; rate changes over a longer continuous period may be more informative. The cancer mortality rates in the 1950-1952 periods in the study counties appear to be abnormally low compared to the US rates; limitations of mortality data may have resulted in underascertainment of cancer cases in these predominantly rural counties. This could be a possible explanation for the increased rate of change in rates between the two time periods. Other possible explanations of the finding include confounding by other variables not assessed, such as smoking, diet and lifestyle changes and role of other known risk factors for various cancers, changes in reporting patterns of mortality data, rapid urbanization, migration patterns, etc. The author's conclusions go beyond the data and the methodology.

8.4.6 Ongoing Studies in Oak Ridge.

Ongoing Studies. Because of the Gardner study[8], NIOSH has funded a similar study in a

U.S. population to provide an independent evaluation of their hypothesis. Dr. Lowell Sever of the Battelle Research Center in Seattle is directing a case-control study of leukemia, non-Hodgkin's lymphoma, and brain tumors in children living near the vicinity of three nuclear facilities: Oak Ridge National Laboratories, Idaho National Engineering Laboratories, and the Hanford nuclear facility. In Oak Ridge, all children diagnosed with leukemia, non-Hodgkin's lymphoma, and brain tumors in Anderson, Roane, and Knox counties between 1957 through 1991 will be identified. Study cases will be restricted to children who were born and residing at the time of cancer diagnosis in one of the three counties, and were also under fifteen years of age at diagnosis. Controls will be selected from the same population base and matched to cases on maternal age, year of birth, and gender. The study subjects (cases and controls) will be linked with the ORR worker files to identify what proportion of them had parents working at the ORR and also to estimate the radiation dose the parents had received prior to conception of the off-spring. The entire data collection relies on the use of existing records. Cases were ascertained through a labor intensive review of records from hospitals (multiple sources within a hospital: tumor registry, medical records, and pathology logbooks) in the three counties and other regional referral centers (Vanderbilt University Medical Center and St. Jude Children's Hospital). Although hospital participation was one hundred percent, missing records were a significant problem. The study is anticipated to be completed by mid-1996.

Table 8-5 Published Ecologic Studies of Mortality in the Population Living Near the Oak Ridge Reservation (ORR)

Study	Type	Population	Exposure	Health Outcome	Comparison Group	Results	Comments
Moshman and Holland, 1949	Morbidity	Oak Ridge residents 1943-48, ?300,000	Geographic proximity to ORR	All cancers and by primary site	U.S. national rates	123.1 cancers/10^5 persons vs 230 per 10^5 national rate	Too short interval between exposure and evaluation of cancer Includes workers and off-site population
Patrick, 1977	Mortality	Residents of Anderson and Roane counties (including city of Oak Ridge) 1929 - 1971; for Oak Ridge 1949-1971	Geographic proximity to ORR	All cancers Fetal Infant Congenital malformation	Tennessee state rates	Trends in crude mortality rates for all cancers increasing parallel to Tennessee; trend evident prior to 1940s; no statistical testing No excess deaths seen by age, gender, or race. Excess leukemia and lung cancers in non-white females in Anderson county (only 2 cases each)	Crude rates, no formal statistical testing
Goldsmith, 1989	Mortality	White children (0-9 years) residing in Anderson and Loudon counties	Geographic proximity to ORR	Leukemia	US national rates	Excess of deaths due to leukemia in 1950-59	Letter to the editor Crude rates, not adjusted for gender ?Loudon county instead of Roane

Study	Type	Population	Exposure	Health Outcome	Comparison Group	Results	Comments
Jablon *et al*, 1991	Mortality	Residents of Anderson and Roane counties, and 6 control counties	Geographic proximity to ORR	All and 16 types of cancer 1950-1984	US national rates 6 matched control counties	No excess of cancer deaths in children <10 years of age, although slightly elevated leukemia deaths. For all ages, 6% and 24% increase in other cancer deaths (excluding leukemia) and cancer of respiratory system compared to control counties, although SMR not increased	Part of national study evaluating 107 counties in/near 62 nuclear facilities compared to 292 matching counties without nuclear facilities. Largest study to date
Mangano, 1994	Mortality	Residents of 94 surrounding counties within 100 miles of ORR	Geographic proximity to ORR	Change in cancer rates from 1950-1952 and 1987-89	US national rates, age and gender adjusted	Significant increases in change in cancer mortality rates for all five hypotheses tested (see text)	? low Tennessee mortality rates in the 1950s Author's conclusions go beyond the data and the methodology

9. Mercury

9.1 Mercury-Description.

Mercury is a naturally occurring element which exists in inorganic and organic forms (or species) which have different properties. Inorganic mercury includes metallic (or elemental) mercury and mercury salts (e.g., mercurous [chloride, nitrate, oxide] and mercuric [sulfide, chloride, acetate, oxide]) salts. Organic mercury exists commonly as methyl mercury and phenyl mercury. The properties of the different species (Table 9-1) are different and thus the health risks associated with exposure varies by species. Metallic mercury is liquid at room temperature and volatile (vaporizes easily), whereas the inorganic salts are solid and generally insoluble but organic mercury is solid and soluble in water.[115]

Metallic mercury is used in chloralkali production, manufacture of electrical and scientific instruments (thermometers, manometers, barometers), extraction of gold from ores, and in dental amalgam fillings. Inorganic mercury salts are used in some lightening creams, topical antiseptics and disinfectants (mercurochrome, thimerosal), and also in batteries. Organic mercury is used as a fungicide (e.g., coating wheat seed to protect from fungus) and also as thinner in some latex based paints in low quantities[115].

Because of its volatility, individuals are exposed to metallic mercury primarily through the inhalation route, with some exposure from the oral and dermal routes. Inorganic salts and organic mercury are exposed to individuals primarily through the oral route, with some through the dermal and inhalation routes. After inhalation, metallic is quickly absorbed (up to 80%) by the lungs and enters the general circulation, whereas it is minimally absorbed from the dermal route and poorly absorbed from the gastrointestinal tract (<.01%). Inorganic mercury salts are poorly absorbed by the gastrointestinal tract (<10% of ingested amount), although mercuric salts are relatively better absorbed. Organic mercury, on the other hand, is completely (100%) absorbed by the gastrointestinal tract. Metallic mercury and its inorganic salts are primarily excreted in the urine and some in the feces, whereas 90% of organic mercury is excreted through the bile and 10% through the urine. The estimated biological half-lives of mercury include 60 days for metallic mercury, 40 days for inorganic mercury salts, and 70 days for organic mercury[115,116].

In the body, metallic mercury can cross the blood-brain and placental barriers and preferentially accumulates in the central nervous system and the kidneys. Inorganic mercury salts cannot cross the biological barriers and preferentially accumulate in the kidneys. Organic mercury easily crosses the blood-brain and placental barriers, and concentrates more in the central nervous system and particularly in the developing fetus. Organic mercury also tends to be deposited in the hair[115-117].

Blood levels of all forms of mercury are good biomarkers for acute exposure, whereas levels in urine are good markers of recent/chronic (up to 3 months) exposure to metallic mercury and its inorganic salts, but not for organic mercury which is not significantly excreted in the urine. Hair is the most reliable biomarker of chronic and also acute exposure to organic mercury[116]. Since hair usually grows one centimeter a month, each centimeter represents the exposure for the

corresponding month, and thus a cumulative exposure dose can be estimated for the length of hair available. Based on human and animal data, the ATSDR established MRLs (minimum risk level) for the different forms of mercury, listed in Table 9-1[115] (see Appendix O).

In the environment, inorganic mercury is biomethylated (slowly) by bacteria in the soil or sediment to form methylmercury[115,117]. The rate of the biomethylation process is not clear, but even if it were very slow, low levels of methyl mercury in the water, nevertheless, can be biomagnified (10,000 - 100,000 fold) and thus possibly be present in fish at much higher levels.

9.2 Characteristics of Mercury Releases in Oak Ridge.

In Oak Ridge, over 11,000 metric tons (24.2 million pounds) of mercury were used to enrich lithium in its Li-6 isotope for use in the production of thermonuclear weapons in the Y-12 plant, primarily from 1955-1963. Because of a sense of national urgency, the entire national stockpile of mercury was shipped to Oak Ridge by an executive order[118]. According to the Department of Energy, an estimated 900 to 1200 metric tons were lost to the environment (320-440 metric tons) or unaccounted for (500 to 860 metric tons). Of the mercury lost to the environment, 23 metric tons were believed to have been lost to the air, 190 metric tons were lost in spills, and 100-210 were released to East Poplar Fork Creek behind the Y-12 Plant, and subsequently into the flood plains of the East Poplar Creek and eventually into the Clinch River. The species of mercury present in the soil of the flood plains is not clear, though it is believed that most of it is in the form of insoluble mercuric sulfide.

9.3 Adverse Health Effects Associated with Mercury.

Organic mercury interacts with a variety of tissues, but has a particular affinity for brain and CNS receptors and renal tubule epithelial cells[119,120]. Inhalation of elemental mercury results in a variety of tissue exposures and has a direct nephrotoxic effect. Furthermore, this inorganic metal is converted to an organic form, methyl mercury. The primary health concerns are adverse effects on childhood development, neurologic impairment, and renal function. A variety of other possible adverse effects have been raised, including dermal/ocular toxicity, respiratory dysfunction, gastrointestinal toxicity, hematologic abnormalities, hepatotoxicity, immune suppression, and adverse reproductive outcomes[115]. However, the biological bases for these concerns are more speculative. Thus, this review is restricted to developmental, neurological, and renal effects.

Table 9-1 Mercury - Summary of Chemical and Biological Properties by Species

Properties	Inorganic Mercury		Organic Mercury
	Metallic (Elemental)	Salts	
Forms	Metallic Hg^0	Hg^+ - mercurous (chloride, nitrate, oxide) Hg^{++} - mercuric (sulfide, chloride, acetate, oxide)	CH_3Hg^- - Methyl mercury $C_6H_5Hg^-$ - Phenyl mercury
State	Liquid at room temperature; volatile	Solid, generally insoluble	Solid, soluble
General Uses	Chloralkali production, electrical /scientific instrumentation (thermometer, manometer, barometer), extraction of gold from ores, dental amalgam fillings	Skin lightening creams, topical antiseptics and disinfectants, batteries	Fungicides, latex paints
Historical Use in Oak Ridge	To enrich lithium in its Li-6 isotope for use in thermonuclear weapons		
Exposure Routes	Primarily inhalation, but also some oral and dermal	Primarily oral, some dermal and inhalation	Primarily oral, but also some dermal and inhalation
Sources of Exposures	Occupational - breathing Hg fumes in Hg-associated industry (chlor-alkali plants) Breathing Hg fumes - spills, incinerators, plants that burn fossil fuels Hg vapors from dental fillings	Ingestion - Hg containing dust and soil, (historically) teething powders Dermal - skin lightening ointments	Primarily through eating contaminated fish and shellfish In infants, through breast milk of exposed mothers
Absorption	Primarily through inhalation - 80% absorbed; poorly absorbed by the gastrointestinal tract (.01%); minimal dermal absorption	Poorly absorbed by the gastrointestinal tract (<10% of ingested amount), some dermal absorption. Mercuric relatively absorbed more than mercurous	100% absorbed through oral route; some through inhalation and dermal also

Properties	Inorganic Mercury		Organic Mercury
	Metallic (Elemental)	Salts	
Excretion	Primarily urine and feces; some through sweat, respiration, and saliva	Primarily urine and feces	90% excreted through bile into feces; 10% in urine
Biological Half-lives	60 days	40 days	70 days
Crosses Blood Brain and Placental Barriers	Yes, rapidly	No (insignificant)	Yes, and concentrated more in blood and brain
Sensitive Target Organs	Central nervous system, kidney	Kidney	Central nervous system, developing fetus
Biological Markers (Exposure)			
Acute Exposure			
Blood (Background 1.5 ug/dl [= 0.07 umol per liter])	Yes	Yes	Yes
Chronic Exposure			
Urine (Background: <20 ug per liter [100 nmol/per liter])	Yes	Yes	No
Hair (Background: <10 parts per million)	No	No	Yes

Properties	Inorganic Mercury		Organic Mercury
	Metallic (Elemental)	Salts	
Reference Levels			
EPA			
Reference Concentration - Inhalation	0.0003 mg/m^3	-	Not determined
Reference Dose - Oral	-	0.0003 mg/Kg/day	0.0003 mg/Kg/day
ATSDR			
Acute inhalation MRL	1.4×10^{-5} mg/m^3	-	-
Chronic inhalation MRL	1.4×10^{-5} mg/m^3	-	-
Acute oral MRL	-	7×10^{-3} mg Hg/Kg/day	1.2×10^{-4} mg Hg/Kg/day
Intermediate/chronic MRL	-	2×10^{-3} mg Hg/Kg/day	

9.3.1 Adverse Developmental Outcomes.

The available data suggest fetal and developmental effects are most pronounced for organic mercury, mainly methyl mercury. Adverse developmental outcomes following oral exposure to organic mercury in several species of laboratory animals during gestation, lactation and/or postweaning have been well established. Increases in several parameters, including birth malformations, (such as, decreased fetal weight, heart defects, smaller brains and dilated ventricles, hydronephrosis) and functional changes (abnormal psychomotor activity) have been well established in several species and effects have been observed at very low exposure levels[115].

The developing nervous system of the fetus is highly sensitive to the toxic effects of organic mercury, which easily enters the fetal circulation after crossing the placenta[117]. The resultant adverse developmental effects of such exposures have been well documented in humans from epidemics of human poisonings, occurring when fish with high levels of mercury have been eaten (e.g., Minamata epidemic, 1955[115,121]) or when grain treated with fungicides containing mercury have been widely consumed (Iraqi epidemic, 1971-72[122]). The symptoms observed in offspring of exposed mothers are primarily neurological in origin and have ranged from delays in motor and verbal development to severe brain damage. Subtle changes, such as small changes in intelligence or learning capacity, have not been extensively tested. Minimum Risk Levels (MRL) (Table 9-1)[115]) for acute- and intermediate-duration exposure to methyl mercury have been developed based on the lowest observed peak hair level in a mother whose child was reported to have a delayed onset of walking (14 ppm in hair)[123] in the Iraqi epidemic.

However, at lower levels of exposure to methyl mercury, the neurodevelopmental effects are less well established, although available evidence indicates that neurobehavioral dysfunction in children may occur if the maternal mercury concentration in hair is >6 μg/g[124]. Two other studies of children, prenatally exposed to methyl mercury, in fish eating populations provide some supporting evidence[115,124]. There are two ongoing prospective studies of children in a fish eating population who have been regularly followed up and assessed since birth (the Seychelles Islands Study and the Faroe Islands Study) for neurobehavioral outcomes associated with prenatal exposures to organic mercury measured by peak maternal hair mercury concentration. These studies should shed some light on the effects of low level exposures of mercury to infant development.

9.3.2 Neurological Effects.

Animal studies have well established the toxic effects of mercury in the central nervous system. Studies show that the cerebellar cortex and dorsal root ganglion cells are particularly sensitive to both inorganic and organic mercury, although the other parts of the brain and peripheral nerves have shown degenerative changes after exposure to methyl mercury. Cats and monkeys are more sensitive to the toxic effects than rodents, and have demonstrated neurological signs at 10 fold lower doses[115].

The nervous system is the primary target organ for elemental and methyl mercury-induced toxicity. Much of the data on neurological and behavioral disorders in humans are from occupational studies where inhalation of metallic mercury vapor has been the main source of exposures[115]. The neurologic and behavioral manifestations associated with mercury exposure encompass a broad range and are non-specific. Specific symptoms include tremors, emotional lability (characterized by irritability, excessive shyness, confidence loss, and nervousness, insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, and muscle twitching), headaches, polyneuropathy (paresthesias, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities), and performance deficits in tests of cognitive and motor function[115,125-133]. However, most of these effects were seen after exposure to high concentrations of mercury vapor, which represents toxicity related to acute tissue exposure to inorganic mercury. These data thus do not necessarily apply to the effects of chronic exposure to much lower doses of organic mercury. There are some data that suggest increased tremors and cognitive difficulties are sensitive manifestations for chronic low-level exposure to metallic mercury vapor[115,129-131] (Table 9-2). However, further data on the effects of low dose chronic exposure to both inorganic and organic mercury are needed.

9.3.3 Renal Effects.

Renal toxicity of both inorganic and organic mercury has been well established in animal studies[115,134]. These studies have clearly demonstrated the primary toxic effects of both inorganic and organic mercury are in the epithelial cells of the renal proximal tubules. Manifestations of the toxicity[133] included proteinuria, oliguria, increases in urinary excretion of tubular enzymes, decreased ability to concentrate urine, and increased serum creatinine. Histopathological changes in the tubules showed eventual fibrosis, inflammation, necrosis, and atrophy to tubules and glomerular changes[115].

Human data on renal toxicity have been primarily based on case series with high exposures due to ingestion of contaminated foods (meat, fungicide treated wheat seeds) and workers occupationally exposed to elemental mercury[115]. Although adverse renal effects following exposure to metallic, inorganic, and organic forms of mercury have been reported, there is no well defined clinical entity. Early manifestations include proteinuria, and depending on the severity of the renal toxicity, hematuria, oliguria, urinary casts, edema, and inability to concentrate urine and may even lead to the nephrotic syndrome (a clinical condition characterized by proteinuria, hypoalbunemia, hyperlipidemia, oval fat bodies and casts in urine, and edema) [115,135]. The condition may rarely even progress to renal failure. However, except with poisoning cases, in the present era with regulated occupational exposures, manifestations of toxicity, if any, are more subtle. With recent advances in diagnostic technology, mild tubular dysfunction may be detected with renal biomarkers, such as retinol binding proteins which are small tubular proteins, instead of with proteinuria which may signify more severe dysfunction.

9.3.4 Ongoing Studies.

Several studies of the neurological and developmental effects of mercury are in progress. The first is the Oak Ridge mercury worker cohort study, a follow-up study of workers who were exposed to elemental mercury from the Y-12 Plant, primarily through inhalation. This is a study being conducted by researchers from Emory University and the Center of Epidemiologic Research of the Medical Sciences Division of Oak Ridge Associated Universities (ORAU), funded by the Centers for Disease Control. In this study workers who had previously been identified in studies conducted by Cragle *et al*[5] and other researchers from Michigan State University are now being recontacted and tested extensively with a wide battery of neurobehavioral tests for neurological deficits related to mercury exposure. This study is currently in the data collection phase. The results of the study should provide further data concerning the long term effects neurological other effects of mercury in this population.

In a population of fish eaters with low exposures to methyl mercury, there are two large ongoing, prospective cohort studies of children who were followed and assessed at regular intervals (at birth, 6, 12, 24, and 36 months, 5 years, respectively) for neurodevelopmental outcomes. These include the Seychelles Islands study of 762 children exposed prenatally to methyl mercury and a similar study from the Faroe islands. Although the findings of these studies are yet to be released, preliminary analyses indicate that no consistent adverse effects were detected at exposures less than 10 ppm of mercury in maternal hair.

Table 9-2 Health Effects Associated With Mercury Levels in Human Blood and Urine (Source: Toxicological Profile of Mercury, ATSDR 1993)

Parameter	Normal levels found in tissue	Observed effect levels	Effect	Reference
Blood (whole)	<0.5-2μg/100 mL			Iyengar et al. 1978
		<1->10μg/100 mL	Increased tremors	Verbeck et al. 1986
		>1.5 μg/100 mL	Disturbances in tests on verbal intelligence and memory	Piikivi et al. 1984
		1.6 μg/100 mL	No effect level for proteinuria	Lauwreys et al. 1983
		1-2 μg/100 mL	Increased prevalence of abnormal psychomotor scores	Roels et al. 1982
		1-2 μg/100 mL	Increased tremors. Impaired eye-hand coordination	Smith et al. 1970
		>3 μg/100 mL	(Estimated threshold level): Increased urinary excretion of β-galactosidase and high molecular weight proteins	Buchet et al. 1980
Urine	0.43-11.4 μg/100 mL			Iyengar et al. 1978
		2-472 μg/g creatinine	Decreased delta-aminolevulinic acid dehydratase and cholinesterase activity. Increased urine coproporphyrin levels	Wade et al. 1969
		3-272 μg/g creatinine	Increased anti-laminin antibodies (implicated in the etiology of autoimmune glomerulo-nephritis)	Lauwreys et al. 1983
		50-100 μg/g creatinine	Increased tremors. Impaired eye-hand coordination	Smith et al. 1970
		>50μg/g creatinine	(Estimated threshold level): Increased urinary excretion of β-galactosidase and high molecular weight proteins	Buchet et al. 1980
		56 μg/g creatinine	No effect level for proteinuria	Lauwreys et al. 1983
		7-1,101 μg/24 hrs	Abnormal memory tests; decreased tibial nerve velocity; increased median nerve latency in both motor and sensory nerves.	Vroom and Greer 1972
		0-510 μg/L	Short-term memory loss	Smith et al. 19

Parameter	Normal levels found in tissue*	Observed effect levels	Effect	Reference
		5-1,000 μg/L	Increased tremor frequency and reaction time; impaired eye-hand coordination	Miller et al. 1975
		<10->1,000 μg/L	Increased tremors	Verbeck et al. 1986
		20-450 μg/L	Increased motor and sensory nerve latency	Levine et al. 1982
		>56 μg/L	Disturbances in tests on verbal intelligence and memory	Piikivi et al. 1984
		100-250 μg/L	Increased acetyl β-D-glucosaminidase (NAG) enzyme levels in urine	Rosenman et al. 1986
		>200 μg/L	Increased tremors; impaired eye-hand coordination	Williamson et al. 1982
		300-1,400 μg/L	Nephrotic syndrome; albuminuria; hypercholesterolemia	Kazantis et al. 1962

* These 'normal' or 'background' levels represent the average levels in urine and blood in the general population, and are not associated with a particular source of mercury. However, the inter- and intra-individual differences in these markers are substantial. These differences may possibly be due to dental amalgam and/or ingestion of contaminated fish[115].

10. Polychlorinated Biphenyls (PCB)

10.1 PCB-Description.

Polychlorinated biphenyls are a family of man-made compounds that are ubiquitous and persistent in the environment. They are synthesized by chlorination of biphenyls leading to the replacement of 1-10 hydrogen atoms by chlorine. The number of chlorine atoms and the position they assume in the biphenyl molecule determine the properties and toxicity of individual congeners, up to 209 of which are known to exist, though only 36 are considered to be environmentally relevant[69,136]. The congeners with more substituted chlorine atoms and those in which the chlorine atoms occupy the parapositions of the biphenyl rings tend to be more stable and not easily metabolized and degraded in the environment. In the US, commercial mixtures are known as Aroclors. Common mixtures include Aroclor 1016, Aroclor 1221, Aroclor 1232, Aroclor 1242, Aroclor 1248, Aroclor 1254, and Aroclor 1260. The four digit codes identify the different Aroclors, with the first two digits (10 or 12) indicating that the parent molecule is biphenyl and the last two digits indicating chlorine content by weight percent.

PCBs exist in an oily form and because of their excellent thermal and chemical stability, have been widely used as dielectric fluids in large, commercial transformers and capacitors and for formulation of lubricating and cutting oils for machining tools. They were also used as plasticizers in paints, carbonless copying paper, adhesives, sealants, and plastics. Because of their reported widespread presence in the environment and the associated health concerns raised primarily from animal studies, PCB production has been banned in the U.S. since the 1970s. Despite overall reduction of PCBs in the environment since, they are still present in large numbers of older commercial capacitors and transformers, and widespread in the environment because of environmental cycling of PCB compounds previously introduced into the environment[69,137].

Exposure to individuals in the occupational setting (commercial capacitor and transformer manufacturing plants) is primarily through inhalation, and some through the dermal route. Exposure to the general population is mainly from ingestion of contaminated food (primarily fish, dairy products) and water, and some through the dermal route by coming in contact with PCB contaminated soil and water (usually during some recreational activity). PCBs are easily absorbed through the gastrointestinal tract if ingested or through the lungs if inhaled, and are distributed throughout the body, preferentially accumulating in adipose (fatty) tissues because of its lipophilic nature and some in the liver. They are metabolized in the liver and excreted mainly in the feces (if ingested) and in the urine (if inhaled). Because of its high fat content, maternal milk has higher concentrations of PCBs and is an important route of excretion. Thus, maternal milk is an important exposure pathway of PCBs for nursing infants. Being lipophilic, PCBs readily cross the blood-brain and placental barriers. Thus, PCBs from maternal blood can readily enter the fetal circulation and accumulate in the developing fetus.

The rates of metabolism and excretion vary by PCB congeners, with the higher chlorinated and those in which the chlorine atoms occupy the parapositions in the phenyl rings generally being

more slowly metabolized and excreted. Thus, these PCB congeners (e.g., Aroclor-1254, -1260) tend to accumulate longer in the body. The biological half-lives of lower chlorinated PCBs (e.g., Aroclor 1242) range from 6-7 months and those of the higher chlorinated ones range from 33-34 months[69,137]. Workers occupationally exposed to PCB mixtures containing low concentrations of the higher chlorinated congeners may have higher concentrations in the body over time. Similarly, in the environment, higher chlorinated compounds degrade more slowly than the lower chlorinated ones. Thus, occupational exposures may be different than environmental exposures for the same PCB mixtures. PCBs also tend to bioaccumulate within the food chain, with bioconcentration factors in aquatic animals varying from 26,000 to 660,000. Thus, even relatively low concentrations of PCBs in water may result in high concentrations in fish, posing a possible health risk (Table 10-1)[69].

Levels of PCB in serum and adipose tissues are good biomarkers of exposure. Serum levels can be useful markers for acute exposure, but the adipose tissues are better markers for long-term exposures, especially for the higher chlorinated congeners and those that lack unsubstituted meta-para position which metabolize slowly and accumulate in fatty tissues. Levels in breast milk are also good markers and have been correlated with PCB contaminated fish. Based on animal data, ATSDR has established a LOAEL (lowest-observed-adverse-effect-level) of .005 mg/kg/day and a MRL (minimal risk level) of 2×10^{-5} mg/kg/day (Table 10-1).

10.2 Characteristics of PCB Releases in Oak Ridge.

In Oak Ridge, PCBs were used as machine coolants and cutting oils in the production of enriched uranium weapon parts at the Y-12 Plant, and the enrichment cascade lubricating oil at the K-25 Plant. The millions of gallons of PCBs used over the years were disposed in a variety of ways, including: in storage tanks some of which leaked, plowed in an 'oil land farm' within ORR, and by burning in incinerators. Significant PCB levels have been identified in the aquatic flora from Watts Bar lake up to the Clinch River[1]. In addition to releases from the ORR, other sources of PCB releases identified include the Bull Run electricity generating plant in the Clinch River upstream from Oak Ridge, and reported land disposal of electrical transformers near Alcoa which resulted in the contamination of a tributary of the Tennessee River.

Table 10-1 Polychlorinated Biphenyls: Summary of Biological and Chemical Properties

	Properties
Forms	Man made; does not occur in natural state Manufactured by chlorination of biphenyls resulting in up to 209 congeners In the U.S., commercial mixtures called Aroclors (Aroclor 1016, -1221, -1232, -1242, -1248, -1254, -1260) Production banned since 1970s Ubiquitous and persistent in the environment
State	Oil, chemically and thermally stable
General Uses	Used as dielectric in transformers and large capacitors, for formulation of lubricating and cutting oils, plasticizers in paints, carbonless copying paper, adhesives, sealants, plastics
Historical Use in Oak Ridge	Used as lubricants in the machining of metal parts and as dielectric fluids in electrical capacitors and transformers
Exposure Routes	Occupational exposure: inhalation mostly, some dermal General population: primarily oral through contaminated food (mainly fish), also contaminated water and soil near hazardous waste sites, some dermal
Sources of Exposures	Occupational: while repairing transformers/capacitors, accidents involving such equipment General population: contaminated fish, hazardous waste sites, incinerators, PCB disposing processes
Absorption	Occupational: inhalation through lungs, some dermal General population: oral through GI tract
Distribution	Lipophilic - concentrated in adipose (fatty) tissue; some in liver, fetus
Excretion	Feces mainly, urine, mother's milk
Biological Half-life	3-24 months (varies considerably by congener)
Crosses Blood Brain and Placental Barriers	Yes
Target Organ	Liver, developing fetus, skin
Biological Markers (Exposure)	Levels in adipose (fatty) tissues, also serum and blood
Reference Levels - *ATSDR* LOAEL Chronic MRL	 .005 mg/kg/day 2×10^{-5} mg/kg/day

10.3 Adverse Health Effects Associated with Polychlorinated Biphenyls.

PCBs are relatively stable compounds which persist in the environment for long periods. PCBs are lipophilic and accumulate and persist in human fat tissues. Thus, because of the potential for very long-term exposure in human populations, there is considerable concern about the health effects of these compounds. Appendix P lists the concentrations of PCBs in U.S. populations with and without occupational exposures. Appendix Q describes summaries of key issues for non-carcinogenic effects and health criteria for PCBs.

Table 10-2 Effects of PCBs on Occupationally Exposed Workers[69]

Effects	Study
Chloracne and related dermal lesions	Fishbein 1979, Hara I 1985, Maroni 1981, Ouw 1976
Diverse hepatic responses, including hepatomegaly, increased liver and serum enzymes	Alvares 1977, Chase 1982, Emmett 1985, Fishbein 1979, Hara I 1985, Lawton 1985, Ouw 1976, Smith JA 1982, Steinberg KK 1986
Decreases in pulmonary function	Warshaw 1979
Decreased birth weight in off-spring of occupationally exposed mothers	Taylor 1984, 1989
Eye irritation	Hara I 1985
No increased mortality	Brown 1981, 1987
Variable effects on cancer formation	Bahn 1976, 1977; Bertazzi 1987, Gustavsson 1986, Sinks 1990, Silberhorn 1990

For high-dose exposures, primarily occupational or poisoning, there are well-established adverse dermo-ocular effects (Table 10-2)[69]. However, of greater concern are the effects of chronic exposure to much lower doses. Studies in animal and *in vitro* models have suggested potential effects that may result from chronic, lower dose exposures. Although a variety of adverse effects have been postulated to be related to PCBs, none of these have been well established[69,138,139]. Although PCBs are known to induce hepatic microsomal enzymes[137] and also affect lipid levels, such as serum cholesterol, the clinical significance of these findings is unclear[69,137]. Those with the greatest degree of plausibility (primarily because of the number of studies with consistent findings) are carcinogenesis and neurodevelopmental effects; however, the evidence is such that this topic remains highly controversial.

10.3.1 Cancer.

The evidence from animal studies indicates that mixtures of PCBs induce preneoplastic lesions and hepatocellular carcinoma in animals when given in appropriate doses for extended periods of time. PCBs mixtures with a high chlorine content (Aroclor-1260) are more potent in inducing neoplastic nodules and hepatocellular carcinomas than mixtures with less chlorination. The neoplasms appear to be relatively unagressive and rarely metastasize. The liver appears to be the target organ for induction of carcinogenicity associated with PCB exposure, but there is some evidence that the stomach, lungs, and skin may also be affected[140]. Based primarily on the animal data, the EPA has classified PCBs as probable carcinogens.

The relatively few studies of cancer in humans have been limited primarily to mortality studies of workers in commercial transformer and capacitor plants exposed occupationally to PCBs[14,76,140-146]. Cancers reported included malignant melanoma, hepatobiliary, brain, and kidney cancers[14,76,140-146]. Although these studies have shown possible association of PCBs with cancer, the findings are inconsistent and inconclusive. This is mainly because of 1) inadequate measurements of PCB exposures, 2) relatively small sample sizes and relatively short follow-up span for rare malignancies, 3) variable quality of data on causes of death, and 4) inadequate control for other concurrent chemical exposures and confounding factors. Furthermore, the types of cancers seen are not consistent with animal models. Nevertheless, follow-up of these cohorts is ongoing and with increased person-years of follow-up, the findings may be more informative.

Because of the postulated estrogenic activity of organochlorines (including DDT and PCBs) which are widespread in the environment, there has been concern of increased risk of breast cancer in women. Several small case-control and cross-sectional studies[9,147-149] that examined the relationship between exposure to environmental organochlorines (DDT and PCB) and the risk of breast cancer found inconsistent results. However, two nested case-control studies of large cohorts of women did not find an increased risk of breast cancer associated with exposure to PCBs[9,14]. Wolff and colleagues[9] conducted a nested case-control study of 58 newly diagnosed cases of breast cancer and 172 matched controls from a cohort of 14,290 women enrolled in the New York University Women's Health Study, a prospective cohort study of hormones, diet, and cancer. PCB exposure (mean PCB serum levels 8.0 ng/mL and 6.7 ng/mL for cases and controls, respectively) was measured from sera from frozen blood specimens of these women obtained at their baseline entry into the cohort (i.e., before development of breast cancer). They found a nearly two-fold but statistically non-significant increase in the relative risk of breast cancer in women with greater than 10.6 ng/mL (90th percentile) compared to those with PCB serum levels less than 3.9 ng/mL (10th percentile). Krieger and colleagues[14] in a larger nested case-control study of 150 cases of breast cancer and 150 matched controls derived from a cohort of 57,040 women did not find an increase in risk of breast cancer associated with exposure to PCBs (measured as in the previous study; mean PCB serum levels 4.4 ppb and 4.8 ppb for cases and controls, respectively).

10.3.2 Developmental Effects.

Developmental effects associated with PCBs administered orally have been tested in several animal species. The most sensitive developmental endpoints appeared to be neurobehavioral deficits, seen in off-spring of monkeys fed low doses of PCB before and/or during gestation and lactation and in off-spring of rats exposed to lower doses of PCB during gestation and lactation[69].

The association between pre- and post-natal exposure of PCBs and subsequent development has been studied extensively in two cohorts of children in the U.S.: the Michigan children cohort and the North Carolina children cohort. In the former cohort, 313 infant-mother pairs were screened for inclusion into the study from 8482 births in hospitals in 15 western Michigan counties bordering Lake Michigan[150]. Since consumption of contaminated Lake Michigan fish was presumed to be the source of PCB exposure, subjects were selected based on their history of fish consumption. Of the 313 mothers, 242 gave a history of consuming >26 lbs of fish in the last 6 years and 71 did not. The mean PCB levels in cord blood were 2.5±1.9 ng/mL, maternal sera 5.5±3.7 ng/mL, and maternal milk 835.9±388.4 ng/mL. Although maternal fish consumption did not correlate with cord PCB levels, it did correlate modestly with maternal sera ($r=0.37$, $p<.001$). The North Carolina cohort included a convenience sample of 930 infants born in 3 hospitals whose mothers were recruited during pregnancy to participate in the study[151]. There were no specific known sources of PCB exposures other than general environmental exposures. The mean maternal PCB serum levels were 9.06 ppb and cord sera level <4.27 ppb (95th percentile 7.49 ppb) with no levels detected in 88% of the specimens.

Baseline and follow-up studies of these two cohorts[150,151] have reported 1) neurodevelopmental effects manifested as motor deficits at birth, 2) impaired psychomotor index during the first year of life[152], 3) impaired visual recognition memory at seven months of age[153], and 4) deficits in short term memory at 4 years of age in those with highest transplacental exposure to PCBs. It is important to note that the deficits represented a statistically significant difference of a few points in the mean scores of the developmental measurement tools used (for example, the Bayley's Scales of Infant Development, McCarthy's Scales of Children's Abilities) but were not clinically obvious. However, these deficits were no longer present at ages 3, 4, and 5 years[150,151]. Review of school performance from report cards in the North Carolina cohort did not show any difference between transplacental PCBs or exposure to PCBs through breast milk[150,151]. Transplacental transfers of PCBs may be significant because of the continuous nature of the exposure even though the breast milk has higher concentrations of PCBs. Consistent with this, Jacobson 1990 did not find neurobehavioral deficits in infants exposed to PCBs from breast feeding, but did so in infants exposed during pregnancy[154].

However, the limitations of these studies, including questionable PCB exposure assessment, selection and comparability of exposed and control subjects[69,139], have raised concerns, making the results of these studies inconclusive. Nevertheless, it is noteworthy that some of the neurobehavioral deficits were observed at levels of PCBs commonly found in the general population in the US. Evaluations of PCBs in blood samples from women who aborted, miscarried, or delivered prematurely have shown associations between these effects and concentrations with PCBs[69].

11. Recommendations

As the main dose reconstruction study progresses, the extent and magnitude of releases and possible human exposure from the current four priority contaminants will be clarified. Identification of the exposed populations and quantitative estimates of their exposure levels obtained from this process will greatly facilitate in evaluating the feasibility, planning and conduct of any future epidemiologic study. It is also possible that one or more of these contaminants may be of lesser significance and instead, some other contaminants may be of greater concern or vice versa. Therefore, the feasibility and desirability of initiating future epidemiologic studies will be significantly influenced by the findings of the main Dose Reconstruction Study (Phase II). The following discussion is based on our review and understanding of the potential health impact from off-site releases of contaminants from the ORR, identified in Phase I of the Dose Reconstruction Study, to the population living near its vicinity.

11.1 Perspective.

As discussed in §2, there is a variety of rationales for conducting epidemiologic studies of the health effects of environmental contaminants. In this discussion, our perspective is that of public health. From this perspective, the motivation for conducting an epidemiologic study is to obtain scientifically valid, quantitative estimates of the adverse health effects of exposures with the goals of:

1. Advancing understanding of the disease causation process, so as to further public health initiatives to reduce risk in the future;

2. Determining and documenting the effects of current and on-going exposure, if any, to facilitate steps to decrease health hazards immediately.

Clearly, there are other motivations for epidemiologic studies. For example, given past exposure of a population to a contaminant with known risk, it might be desirable to quantify health effects for medicolegal purposes. Although such a perspective is not taken here, the approach taken is nevertheless applicable. The techniques outlined in §3 through §6 can be utilized to judge the feasibility of such studies.

11.2 Criteria for Initiating Epidemiologic Studies.

Because of the difficulty and expense of conducting scientifically valid epidemiologic studies with a public health perspective, such studies should only be initiated after careful consideration of the rationale and possible return. Each specific contaminant-health outcome pair must be carefully assessed. Although determining whether to initiate a study always requires a large component of judgement, there are several broad criteria that can be applied. These are

outlined below.

1. **Material potential exposure of the population to the contaminant.** If only a small number of persons were potentially exposed or the levels of exposure were sufficiently low, then the question is of more limited public health relevance;

2. **Reasonable scientific basis for concern.** The rationale for concern might consist of:

   a. Biological effects of the contaminant, such as chromosomal damage;
   b. Animal studies, such as increased tumerogenicity;
   c. Human studies, including suggestive epidemiologic studies, case series, etc.

3. **Material scientific uncertainty regarding actual health effects.** Given a basis for concern, there needs to be uncertainty regarding the actual health effects. If there is reasonable certainty that the exposure is harmful, then public health activity should be directed at reducing exposure rather than further study. However, this criterion may not apply in some situations. For example, if the purpose of a study were to determine and document what happened to persons (in terms of health effects) exposed to a contaminant in the past, one may do the study regardless of the scientific certainty that exposure to the contaminant causes disease. Similarly, there could be reasonable certainty that an exposure (in general terms) is harmful, but more subtle effects - which could be important in practical terms - could well require further study. Although this criterion should be considered, it is of lesser significance than criteria 1 and 2 above.

4. **Feasibility and cost of study.** Even studies that meet 1-3 above may not be feasible, for example, because of inadequate sample size and availability of data sources. Studies that are in theory feasible may have excessive costs that may not be justifiable given the health effect of concern and/or limited available resources.

11.3 Iodine-131.

For this contaminant, there was clearly wide population exposure at some level, a reasonable basis for concern of increased risk of thyroid disease above certain exposure levels, and yet, a reasonable scientific uncertainty about the association between ^{131}I and thyroid disease. Thus, although this contaminant meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, as discussed below.

Based on Phase I results of the Dose Reconstruction Study, an estimated 300,000 Ci of ^{131}I (estimated releases from the Hanford Reservation were 740,000 Ci of ^{131}I) was released from the RaLa operations in the X-10 facility from 1944 to 1956. However, the amount of ^{131}I releases

may be significantly lower (<100,000 Ci), based on more recent Phase II data. Because of a very short radioactive half-life of 8 days, ^{131}I did not persist in the environment and so is not a current exposure hazard. However, based on the initial magnitude of ^{131}I releases, it is possible that some historically exposed individuals may have developed thyroid disease.

As described in Appendix M, the Fred Hutchinson Cancer Research Center in Seattle under the direction of Dr. Scott Davis is currently conducting a CDC-funded, retrospective cohort study of ^{131}Iexposure and thyroid disease in Hanford, Washington State, called the Hanford Thyroid Disease Project. This is a state of the art study using dosimetry data to estimate individual radiation doses to study dose-response effects. The study has set up a comprehensive logistical framework to trace and locate individuals, identified from birth certificates, born nearly 50 years earlier and and to interview them (and their parents) in great detail and to conduct a comprehensive clinical examination of the thyroid gland. It has now been established in a two year pilot study that this design is clearly feasible, and should serve as a model for any future epidemiologic study of this issue in the Oak Ridge setting.

The final results of the Hanford Thyroid Disease Study are expected to be released in mid-1998. We thus recommend that the Panel not consider such a study in Oak Ridge, at present. A similar study in Oak Ridge would be duplicative, very expensive (cost of the Hanford Study is an estimated $16 million), and unlikely to provide new scientific insight. However, the latter point may be less relevant if the main purpose of an epidemiologic study at Oak Ridge were simply to demonstrate whether people who were significantly exposed developed any adverse health effects. As an alternative to a large epidemiologic study, the Hanford dose-response results could be used to characterize risk to the Oak Ridge exposed population.

An alternative interim approach that we considered and rejected is the use of the Tennessee Medicaid database to identify individuals (from diagnostic codes of claims data and through Synthroid prescriptions from pharmacy files) with clinical thyroid disease (hypothyroidism, neoplasms, and others) and compare rates by county of residence and age from 1975 through 1993. We concluded that such a study would be uninformative and uninterpretable for several reasons. First, hypothyroidism and thyroid neoplasms are substantially underdiagnosed, leading to the possibility of bias because of underascertainment and differential ascertainment because of factors that lead to diagnosis and treatment (such as awareness of radiation effects by individuals as well as providers). Second, the Medicaid population is not representative of the general population and may differ by county, making comparisons and generalizability murkier. Third, the small sample size (number of Medicaid enrollees from Anderson, Roane, and Loudon counties ranged from 9,356 in 1975 to 21,330 in 1993) limits the power of the study to detect even moderate differences in rates. Finally, the cross-sectional nature of such a study would face the inherent limitations of such designs.

11.4 Cesium-137 and Other Radionuclides.

11.4.1 Outcomes

Although results of the dose-reconstruction study are needed, it seems that the potential for wide exposure to low levels of ionizing radiation from these radionuclides is present. Furthermore, there is a basis for concern for several radiation-linked cancers, primarily acute leukemias, and neurodevelopmental (microcephaly, mental retardation, such as lower IQ) and birth defects. Despite this basis for concern, there is no scientific certainty that the low level doses probably characteristic of the exposures in the Oak Ridge catchment actually increase risk of these diseases. Thus, although this group of contaminants meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, which are considered separately for retrospective and prospective study designs.

Retrospective Cohort Study. Retrospective cohort studies are attractive because they are the most economical among cohort designs. However, the primary difficulty is in defining study groups (i.e., the cohort) without estimates of exposure that occurred in the remote past and for which there are no individual records of exposure. The findings of the dose reconstruction study and the attendant uncertainty analysis should allow for defining groups of people who were exposed, exposed at various levels, or unexposed. Thus, pending further information from the dose reconstruction study, retrospective cohort studies do not appear feasible because of the absence of valid past exposure data.

Prospective Cohort or Nested Case Control Study. Many of the health outcomes of concern discussed above could be addressed by large prospective cohort studies or nested case-control studies within the cohort. However, the main difficulty is in constructing a cohort to follow based on current and on-going exposures to radionuclides. Although there are biomarkers, such as frequency of chromosomal aberrations in the peripheral lymphocytes[21], for recent exposure to radiation, they are of limited practical use in large epidemiologic studies and are also not specific to individual radionuclides. Furthermore, use of chromosomal aberrations in lymphocyte may not be applicable for low doses of radiation. However, this being a rapidly evolving discipline, valid biomarkers of practical use may be available in the future. Prospective studies would also need to encompass large numbers (in the thousands) of persons in the catchment area. Furthermore, given the latency periods for some of the cancers, decades of follow-up would be required. Thus, unless the dose reconstruction study shows high current exposure levels, prospective studies are probably not warranted.

11.5 Mercury.

11.5.1 Outcomes.

Outcomes of concern for mercury are childhood intellectual and motor development, neurologic toxicity, and renal toxicity. There is possible wide distribution of the contaminant, a scientific basis for concern, yet genuine scientific uncertainty at lower levels of exposure. Thus, although mercury meets criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues are feasibility and cost, which are considered separately for retrospective and prospective study designs.

Retrospective Cohort Studies. As discussed for radionuclides, retrospective cohort studies may not be feasible, primarily because of the difficulty in defining population groups who were exposed in the past and the lack of well-defined health effects associated with low levels of exposure. To the best of our knowledge, there are no reliable biomarkers of historical mercury exposures. We also are unaware of any systematic set of stored biological specimens (bloods, tissues etc) that could be used for exposure definition. The findings of the dose reconstruction study and the attendant uncertainty analysis should allow for defining groups of people who were exposed, exposed at various levels, or unexposed. Thus, pending further information from the dose reconstruction study, retrospective cohort studies do not appear feasible. Furthermore, health effects related to low level, chronic exposures to mercury do not present as well defined 'clinical syndromes' that can be easily ascertained retrospectively. For example, it would be infeasible to retrospectively ascertain intention tremors or memory loss, established effects of mercury exposure, from medical records. Even with information from the dose reconstruction study, a retrospective study would pose enormous problems.

Prospective Cohort or Nested Case-Control Studies. It would be difficult to conduct adequately large prospective studies or nested case-control studies of adults. Of major concern are the need to obtain specimens from large numbers of subjects, the need for intensive prospective monitoring to obtain outcome information, the lack of well identified outcomes thus necessitating broad and potentially insensitive screening, and the substantial population variance in outcome measurements such as cognitive functioning. Further information may be provided by the ongoing Oak Ridge occupational cohort study of mercury exposed workers.

Infants may be more susceptible to the intellectual and motor developmental effects of organic mercury. Furthermore, prenatal exposure to mercury can be reliably measured from maternal hair, and several age-appropriate standardized scales of infant development are now available for measuring outcomes. Thus, such studies may have higher priority in this population. However, given the uncertain correlation between contaminant release and material tissue exposure, such studies may yet be premature. Thus, our recommendation is to defer such studies pending the bioprevalence study (see §11.7).

11.6 Polychlorinated Biphenyls.

11.6.1 Outcomes

Similar considerations are present for PCBs. Outcomes of concern for PCBs include childhood intellectual and motor development, and cancer (although which specific type is not clear). There is possible wide distribution of the contaminant, a scientific basis for concern, yet genuine scientific uncertainty at lower levels of exposure. Thus, although PCBs meet criteria 2-3 and possibly 1 described above for considering an epidemiologic study, the major issues again are feasibility and cost, which are considered separately for retrospective and prospective study designs.

Retrospective Cohort Studies. As discussed for radionuclides, retrospective cohort studies may not be feasible, primarily because of the difficulty in defining population groups with exposure in the remote past. Although the half-lives of some higher chlorinated PCBs have been reported to be as long as 17 years in fatty tissues, we are not aware of reliable biomarkers of practical use to measure historical PCB exposures. We also are unaware of any systematic set of stored biological specimens (bloods, tissues etc) that could be used for exposure definition. Thus, pending additional findings of the dose reconstruction study, retrospective cohort studies do not appear feasible because of the absence of valid past exposure data.

Prospective Cohort or Nested Case Control Study. PCBs and its association with cancer could be addressed by large prospective cohort studies or nested case-control studies (within the cohort) of adults. However, these studies would need to encompass large numbers (in the thousands) of persons in the catchment and would require prospective determination of exposure, through biomarkers of recent exposure, such as blood PCB levels. Although PCB levels in fatty tissues would be the preferred biomarker for exposure, the invasive nature in obtaining specimens limits its practical utility, although it is feasible. However, this would be extremely expensive. Furthermore, given the latency periods for many cancers, decades of follow up would be required. Thus, unless the dose reconstruction study or bioprevalence study (see §11.7) shows high exposure levels, prospective studies of PCBs and its association with cancer are probably not warranted at present.

As with mercury, infants may be more susceptible to the intellectual and motor developmental effects of PCBs. Furthermore, prenatal exposure to PCBs can be reliably measured from maternal blood and cord blood, and several age-appropriate standardized scales of infant development are now available for measuring outcomes. Thus, such studies may have higher priority in this population. However, given the uncertain correlation between contaminant release and material tissue exposure, such studies may yet be premature. Thus, our recommendation is to defer such studies pending the bioprevalence study (see next).

11.7 Recommendation: Bioprevalence Study.

Based on Phase I results of the Dose Reconstruction Feasibility Study, three of the priority contaminants (mercury, polychlorinated biphenyls, and radionuclides such as ^{137}Cs) are still persistent in the environment, primarily in aquatic biota and sediment beds of the Clinch River and the Watts Bar Reservoir. The main sources of releases were from the Y-12 facility into East Fork Poplar Creek and its flood plains for mercury, from the X-10 facility to White Oak Creek for ^{137}Cs and the other radionuclides, and from the K-25 plant to the Clinch River and at least three other upstream sources for PCBs. Ultimately, all three contaminants drain into the Clinch River which in turn drains into the Tennessee River before Watts Bar Dam. The long half-life of ^{137}Cs (30 years) and the persistence of both mercury and PCBs mean that they continue to persist in the environment and continue to be of potential risk for humans.

However, for each of the contaminants considered, a crucial question is the level of current exposure in the population. If a large number of persons have high exposure levels then epidemiologic studies are warranted, though they may not always be feasible. Although the dose reconstruction studies and uncertainty analysis are the only practical way to obtain information on past exposures, current exposure can be assessed with bioassay, particularly for mercury and PCBs. The samples obtained for such assays can be preserved, which would permit future studies as assay techniques improve or if there are new contaminants of concern.

Thus, a bioprevalence study should be considered. The study could focus on one or more defined population groups. Studies of infant-mother pairs while in hospital and adults could be investigated. Infant-mother pairs could be identified from the birthing facilities most likely to be used by the population at risk (e.g., Methodist Medical Center of Oak Ridge) over a defined period of time. For adults, a random sample of the population could be surveyed. Sampling could be stratified by areas believed to be more contaminated to insure selection of individuals at higher risk for exposure.

The surveys should encompass both the Oak Ridge area and another region in Tennessee, as a control group, to be surveyed concurrently. A control group in another Tennessee population, matched on several population characteristics (e.g., proportion of population that are white, black, urban, rural, high school graduates; mean family income, population, mortality and infant mortality rates) is desirable to address the issue of whether the population of the Oak Ridge area is at higher risk from exposure to these contaminants than a comparable population. Although comparison with existing population reference standards alone is an alternate option, this has the potential for biases introduced by incomparability of populations, time trends in environmental levels of contaminants and measurement techniques. Thus, a separate comparable control population should be surveyed concurrently to minimize such biases. On the other hand, if the study objective were to simply evaluate the levels of exposure to a contaminant at which adverse health effects can be demonstrated in the Oak Ridge population, subjects with no/minimal exposures would serve as the reference group and an independent comparison group would not be necessary. However, our understanding is that this is not the main objective.

Samples of hair, urine, and blood could be obtained and multiple contaminants (PCBs,

mercury) assessed. In addition, data can be collected on demographic characteristics, health status, dietary (such as, fish consumption for mercury and PCBs) and other potential sources (such as, recreational activities, occupation, and use of dental amalgam for mercury) of exposures from survey questionnaires of subjects.

The major advantages of this approach are that 1) it is a first step in addressing current public health concerns in a scientifically valid method, 2) levels of current contaminants can be directly measured in individuals which can help prioritize contaminants of greater concern, 3) multiple contaminants can be measured, 4) specimens can be stored, so that prevalence levels of contaminants of concern identified in the future can be measured and/or as better assay techniques are developed, the current contaminants can be reassessed, 5) it can provide needed information on exposure levels and dose variances to calculate sample size and power for future studies, and 6) it can be used to validate the models used for exposure or body burden assessment or to check the accuracy of predictions made by such models. Given the length of time and large amount of resources required to conduct a meaningful epidemiologic study, a bioprevalence study would be an important starting phase, before other studies are considered.

Contingent on the findings of such a survey and availability of funding, for example, a prospective long-term, cohort study of newborn infants for birth defects and neurodevelopmental outcomes could be considered. Exposures from the contaminants (radionuclides, organic mercury, and PCBs) discussed above appear to share similar pathways with considerable overlap of the resultant exposed population. There is concern that prenatal exposure to these contaminants may adversely affect the fetus which may manifest in neurodevelopmental effects in infancy and childhood. Thus, such a study has the potential advantage of being able to evaluate the association between exposure to multiple contaminants and risk of a common health effect (neurodevelopmental) in a susceptible population, such as newborns. Furthermore, unlike adults, there is no temporal ambiguity between exposure and development of adverse health effects. The initial bioprevalence survey would provide precise, current exposure levels of contaminants in the population, and assist in determining sample size requirements for these type of studies.

11.8 Interface Between Epidemiology and Dosimetry.

As more information becomes available from the dose reconstruction study regarding estimates of exposure doses from a given contaminant and the size of the exposed population, the epidemiologist and the dose reconstruction contractors will need to work closely together to explore the feasibility of initiating a study. Preliminary estimates of dose and definition of the exposed population provided by the contractor can be used by the epidemiologist/biostatistician to calculate sample size and power of a study. Such calculations must be based on specific outcomes associated with the contaminant in specific population subgroups, and the epidemiologist should provide the dosimetry contractors his/her needs for performing such calculations. For example, in a study of ^{131}I and thyroid disease, where the defined subgroup of interest includes persons who were exposed as infants and small children and where there is a nearly three-fold higher effect in females, preliminary dose estimates and their uncertainty by these

age groups and by gender would be needed. Furthermore, if a decision to proceed with an epidemiologic study is made, individual dose estimates would be needed, and the epidemiologist would need to work closely together with the dosimetry team to decide on important parameters (quantity of milk consumed, residence history, outdoor activity. etc. for ^{131}I exposure) for estimating individual doses and develop questionnaires to collect such data. Thus, there is an ongoing need for active epidemiologic support for the Oak Ridge Health Studies.

11.9 Investigation of Clusters of Health Events.

Investigation of Reported Clusters. The main thrust of the Oak Ridge Health Studies has been contaminant driven. That is, a specific contaminant with significant off-site releases to which the population may be exposed is first identified. The risk of adverse health effects associated with exposure to such a contaminant is then assessed. However, there may be reports from the public of possible clusters of some diseases or illness, independent of this process, that the State Health Department may need to respond to. A good example is the current investigation of a possible cluster of amyotrophic lateral sclerosis (ALS) in the Oak Ridge area, which was reported by members of the public. In order to systematically be able to respond to such reports, we recommend that an excellent monograph published by the Centers for Disease Control in its *Morbidity and Mortality Weekly Review Supplement* in August 1990 be used as a framework for developing a tailored protocol. A copy of this monograph entitled "Guidelines for Investigating Clusters of Health Events" is attached as Appendix R. The dose reconstruction and bioprevalence studies will help further define the probability that future cluster outbreaks are linked to contaminants.

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Glossary of Common Epidemiologic Terms

Adjustment: a procedure for overall comparison of two or more populations in which background differences in the distribution of covariables are removed.

Age adjustment: a procedure used to calculate summary rates for different populations in which underlying differences in the age distributions are removed.

Age standardization (direct): a procedure for obtaining a weighted average of age-specific rates in which the weights are selected on the basis of a standard age distribution (eg, the population of the United States in 1940).

Analytic epidemiology: activities related to the identification of possible determinants of disease occurrence.

Analytic study: a research investigation designed to test a hypothesis that is often used in reference to a study of an exposure-disease association.

Association: the extent to which the occurrence of two or more characteristics are linked either through a causal or noncausal relationship.

Attributable risk percent: the percentage of the overall risk of a disease outcome within exposed persons that is related to the exposure of interest.

Bias: a non-random error in a study that leads to a distorted result.

Case: a person who has a disease of interest (see also Incident case and Prevalent case).

Case-control study: an observational study in which subjects are sampled based on the presence (cases) or absence (controls) of the disease of interest. Information is collected about earlier exposure to risk factors of interest.

Causality: the extent to which the occurrence of a risk factor is responsible for the subsequent occurrence of a disease outcome.

Clinical trial: an experimental study that is designed to compare the therapeutic benefits of two or more treatments.

Cluster: a group of cases of a disease that are closely linked in time, place of occurrence , or both.

Cohort: a group of persons who share a common attribute, such as birth in a particular year or residence in a particular town, who are followed over time.

Cohort study: an observational study in which subjects are sampled based on the presence (exposed) or absence (unexposed) of a risk factor of interest. These subjects are followed over time for the development of a disease outcome of interest.

Confidence interval: a range of values for a measure that is believe to contain the true value within a specified level (eg, 95%) of certainty.

Confounder: a variable that distorts the apparent relationship between an exposure and a disease of interest.

Confounding: a systematic error in a study that arises from mixing of the effect of the exposure of interest with other associated correlates of the disease outcome.

Control: in a case-control study, a subject without the disease of interest.

Control group: a population of comparison subjects in an analytic investigation.

Correlation study: a hypothesis-generating investigation in which the values of two or more summary characteristics are associated across different population group.

Cross-sectional study: an analytic investigation in which subjects are sampled at a fixed point or period of time, and then the associations between the concurrent presence or absence of risk factors and diseases are investigated.

Cumulative incidence: the risk of developing a particular disease within a specified period of time.

Descriptive epidemiology: activities related to characterizing patterns of disease occurrence.

Differential misclassification: incorrect categorization of the status of subjects with regard to one variable (eg, exposure) that is influenced by other characteristics of interest (eg, disease status).

Dose-response relationship: an exposure-disease association in which the risk of disease varies with respect to the intensity or duration of exposure.

Ecologic fallacy: an association between summary characteristics across populations without actual linkage of the characteristics within individual persons.

Endemic rate: the usual rate of occurrence of particular events within a population.

Epidemiology: the study of the distributions and determinants of disease within human populations.

Excess risk: the extra risk of a particular disease occurring among persons exposed to a risk factor of interest.

Exposure: contact with or possession of a characteristic that is suspected to influence the risk of developing a particular disease.

External validity: the extent to which the conclusions of a study are correct for persons beyond those who were investigated .

False-negative: a test result that is normal (negative) despite the true presence of a particular disease or a study result that incorrectly fails to identify a true effect (see also Type II error).

False-positive: a test result that is abnormal (positive) despite the true absence of the disease of interest or a study result that incorrectly indicates an effect, when if truth, the effect does not exist.

Generalize: the ability to extrapolate study results from the study subjects to other persons who were not investigated.

Historical controls: subjects in a clinical study who were previously treated with the standard therapy before the new treatment was introduced.

Hypothesis-generating study: an exploratory investigation designed to formulate questions that are evaluated in subsequent analytic studies.

Hypothesis-testing study: an analytic investigation in which one or more specific refutable suppositions is (are) evaluated.

Incidence rate: the rapidity with which new cases of a particular disease arise within a given population.

Incident case: a person who is newly diagnosed with a disease of interest.

Independent variable: a factor that is suspected to influence the outcome of an analytic study.

Information (or observation) bias: a systematic error in a study that arises from the manner in which data are collected from participants.

Internal validity: the extent to which the conclusions of a study are correct for the subjects under investigation.

Latent period: time between exposure to a risk factor and subsequent development of clinical manifestations of a particular disease.

Matching: a procedure for sampling comparison subjects based upon whether key attributes (ie, matching factors) are similar to those of subjects in the index group.

Misclassification bias: incorrect characterization of the status of subjects with regard to a study variable that leads to a distorted conclusion.

Mortality rate: the rapidity with which persons within a given population die from a particular disease.

Non-differential misclassification: incorrect categorization of the status of subjects with regard to one variable (eg, exposure) that is unrelated to another characteristic of interest (eg, disease status).

Null value: the point on the scale of a measure of association that corresponds to no association (eg, 1 for the risk ratio and the odds ratio, and 0 for the risk difference and the attributable risk percent).

Observational study : a nonexperimental analytic study in which the investigator monitors, but does not influence, the exposure status of individual subjects and their subsequent disease status.

Odds: the probability that a particular event will occur divided by the probability that the event will not occur.

Odds ratio: the odds of a particular exposure among persons with a specific disease by the corresponding odds of exposure among persons without the disease of interest.

Outcome variable: in an analytic study, the response of interest (eg, development of disease).

Person-time: a unit of measurement used in the estimation of rates that reflects the amount of time observed for persons at risk of a particular event.

Population at risk: persons who are susceptible to a particular disease but who are not yet affected.

Population-based study: an analytic study in which subjects are sampled from the general population.

Positive predictive value: the probability that a person with a positive (abnormal) test result actually has the disease of interest.

Precision: the extent to which a measurement is narrowly characterized. Statistical precision is inversely related to the variance of the measurement.

Prevalence: the proportion of persons in a given population who have a particular disease (new and old) at a point or interval of time.

Prevalent case: a person who has a disease of interest that was diagnosed in the past.

Prospective cohort study: a cohort study in which exposure status and subsequent occurrence of disease both occur after the onset of the investigation.

Randomization: procedure for assigning treatments to patients by chance.

Rate: the rapidity with which health events such as new diagnoses or deaths occur.

Rate ratio: the rate of occurrence of a specified health event among persons exposed to a particular risk factor divided by the corresponding rate among unexposed.

Reliability: the extent to which multiple measurements of a characteristic are in agreement.

Retrospective cohort study: a cohort study in which exposure status and subsequent development of disease both occur prior to the onset of the investigation.

Risk: the probability that an event (eg, development of disease) will occur within a specific period of time.

Risk difference: the risk of a particular disease occurrence among persons exposed to a given risk factor minus the corresponding risk among unexposed persons.

Risk factor: an attribute or agent that is suspected to be related to the occurrence of a particular disease.

Risk ratio: the likelihood of a particular disease occurrence among persons exposed to a given risk factor divided by the corresponding likelihood among unexposed persons.

Sample: a subset of a target population that is chosen for investigation.

Screening: the use of tests to detect the presence of a particular disease among asymptomatic persons prior to the time that the disease would be recognized through routine clinical methods.

Selection bias: a systematic error in a study that arises from the manner in which subjects are sampled.

Sensitivity: the probability that a person who actually has the disease of interest will have a positive (abnormal) test result.

Specificity: the probability that a person who actually does not have the disease of interest will have a negative (normal) test result.

Standardization: an analytic procedure for obtaining a summary measure for a population by applying standard weights to the measures within sub-groups of the population.

Statistical power: the ability of a study to detect a true effect of a specified magnitude. The statistical power corresponds to 1 - Type II error.

Statistical significance: the likelihood that a difference as large or larger than that observed between study groups could have occurred by chance alone in a sample of the size investigated. Usually, the level of statistical significance is stated as a *P*-value (eg, $P<0.05$).

Surveillance: ongoing observation of a population for rapid and accurate detection of changes in the occurrence of particular diseases.

True-negative: a test result that is normal (negative) when the disease of interest is actually absent.

True-positive: a test result that is abnormal (positive) when the disease of interest is actually present.

Type I error: rejection of the null hypothesis when it is actually correct.

Type II error: failure to reject the null hypothesis when it is actually incorrect.

Validity: the extent to which a measurement or a study result correctly represents the characteristics or relationship of interest.

Vital statistics: information concerning patterns of registered life events, such as births, marriages, divorces, and deaths.

Glossary of Some Common Terms

Acute Exposure	Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.
Bioconcentration Factor (BCF)	The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.
Cancer Effect Level (CEL)	The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.
Carcinogen	A chemical capable of inducing cancer.
Chronic Exposure	Exposure to a chemical for 365 days or more, as specified in the ATSDR Toxicological Profiles.
Developmental Toxicity	The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.
Embryotoxicity and Fetotoxicity	Any toxic effect on the conceptus as a result of prenatal exposure to the chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.
In Vitro	Isolated from the living organism and artificially maintained, as in a test tube.
Reproductive Toxicity	The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.
Teratogen	A chemical that causes structural defects that affect the development of an organism.
Uncertainty Factor (UF)	A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.
Lethal Dose$_{(50)}$ (LD_{50})	The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.
Lowest-Observed-Adverse-Effect Level (LOAEL)	The lowest dose of chemical in a study, or group of studies, that produced statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.
Malformations	Permanent structural changes that may adversely affect survival, development, or function.
Minimal Risk Level	An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.
Mutagen	A substance that causes mutations. A mutation is a change in a genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.
Neurotoxicity	The occurrence of adverse effects on the nervous system following exposure to chemical.
No-Observed-Adverse-Effect Level (NOAEL)	The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.
Reference Dose (RfD)	An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) be a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Absorbed Dose (or radiation)	The energy imparted by ionizing radiation per unit mass of irradiated material. The units of absorbed dose are the rad and the gray (Gy).
Acute	Of short duration and/or rapid onset. An acute toxic effect is one that develops during or shortly after a brief exposure to a toxic substance.
Becquerel (Bq)	The International System of Units (SI) unit of radioactivity. One becquerel equals 1 disintegration per second. One curie equals 3.7×10^{10} Bq.
Chronic Exposure	Repeated exposure to a chemical for over 3 months.
Committed Dose Equivalent ($H_{T,50}$)	The dose-equivalent to organs or tissues of reference (T) that will be received from an intake of radioactive material by an individual during the 50-year period following intake.
Dermal	Related to the skin.
Dose (for chemical toxicants)	The amount of a substance available for interaction with metabolic processes of an individual following exposure and absorption. The amount of a substance crossing the exchange boundaries of the skin, lungs, or digestive tract is termed absorbed dose.
Dose (radiological dose)	A generic term that means absorbed dose, dose equivalent, effective dose equivalent, or committed effective dose equivalent.
Dose Equivalent (H_T)	The product of the absorbed dose in tissue, a quality factor, and all other necessary modifying factors at the location of interest. The units of dose equivalent are the rem and the sievert (Sv). 1 Sv = 100 rem.
Effective Dose Equivalent (H_E)	The sum of the products of the dose equivalent to the organ or tissue (HT) and the weighting factors (WT) applicable to each of the body organs or tissues that are irradiated ($H_E = \sum W_T H_T$)
Epidemiology	The study of the distribution and causes of diseases and injuries in human populations.
Exposure	In general terms, the amount of a chemical substance or radiation in the vicinity of a portal of entry to the body (e.g., the lungs, mouth, skin) that may be available for absorption. Exposure is also a measure of the ionization produced in air by X or gamma radiation. The special unit of radiation exposure is the roentgen (R).
Fission	The splitting of a nucleus into at least two other nuclei with the release of 1-5 neutrons and a relatively large amount of energy.
Fission Products	The nuclei (fission fragments) formed by the fission of heavy elements, plus the nuclides formed by the fission fragments' radioactive decay.
Half-Life (physical)	The time in which half the atoms of a particular radioactive substance disintegrate to another substance.
Half-Life (effective)	The time required for a radioactive element in an animal body to be diminished 50 percent as a result of the combined action of radioactive decay and biological elimination.
Inorganic	Chemical substances which do not contain carbon linked to other elements by covalent bonds. Inorganic refers to chemical substances that are not hydrocarbons or their derivatives. For example, carbides, carbonates, and elemental metals are inorganic substances.
Insoluble	Not able to be dissolved in a fluid (as in the term "water insoluble")
Isotopes	Nuclides having the same number of protons (same atomic number, and therefore same element) but differing in their number of neutrons and therefore their mass numbers (number of protons plus neutrons). Often, particularly in the past, improperly used as a synonym for nuclide.
Lesion	Generic term for a type of damage or alteration. For example, abrasions, blisters, ulcers, dermatitis, and skin cancer are all types of skin lesions.
Malignant	In reference to cancer, having the property of uncontrollable growth and dissemination, or recurrence after removal, or both.
Melanoma	A malignant lesion that may occur in the skin of any part of the body, in the eye, or in mucous membranes. Melanomas often originate in a pigmented mole.
Nuclide	An individual species of an element characterized by its particular mass number (number of protons plus neutrons), atomic number (number of protons), and the energy state of its nucleus.

Organic	Chemical compounds which contain carbon atoms linked by covalent bonds.
Pathological	Altered or caused by disease
Radioactive	Possessing the property of spontaneously emitting electromagnetic rays or charged subatomic particles of matter with the release of energy.
Radionuclide	A radioactive nuclide.
Reference Concentration (RfC)	A concentration (mg/m3) of a chemical in air that is not expected to cause adverse health effects over a lifetime of daily exposure. The term "reference concentration" refers to the concentration of a chemical in air that is inhaled.
Risk	The nature and probability of occurrence of an unwanted, adverse effect on human life or health, or on the environment.
Sievert (Sv)	The special name for the International System of Units (SI) unit of dose equivalent. 1=Sv=1 J/kg=100 rem.
Slope Factor (SF)	The 95 percent upper confidence limit of the probability that a carcinogenic response will occur per unit daily intake of a chemical over a lifetime. Slope factors for most chemicals are expressed in units of $(mg/kg\text{-}day)^{-1}$. The slope factor for asbestos is expressed in units of $(fibers/ml)^{-1}$.
Soluble	Able to be dissolved in a fluid (as in the term "water soluble")
Toxicity	The degree to which a substance causes change in an organism which results in impairment of function or enhances susceptibility to the harmful effects of other environmental influences.
Volatilize	To evaporate or cause to evaporate. The conversion of a solid or liquid into a gas.