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# CIRRPC

## Science Panel Report No. 6

# USE OF PROBABILITY OF CAUSATION BY THE VETERANS ADMINISTRATION IN THE ADJUDICATION OF CLAIMS OF INJURY DUE TO EXPOSURE TO IONIZING RADIATION

**August 1988**

Committee on Interagency Radiation

Research and Policy Coordination

Office of Science and Technology Policy

Executive Office of the President

Washington, D.C. 20506

The Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) is chartered through the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), Office of Science and Technology Policy, Executive Office of the President, Washington, D.C. 20506.




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COMMITTEE ON INTERAGENCY RADIATION RESEARCH
AND POLICY COORDINATION
1019 Nineteenth Street, NW, Suite 700
Washington, D.C. 20036
August 10, 1988

Mr. Thomas K. Turnage
Administrator of Veterans Affairs
Veterans Administration
810 Vermont Avenue, N.W.
Washington, DC 20420

Dear Mr. Turnage:

I am pleased to forward a report by the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) titled "The Use of Probability of Causation by the Veterans Administration in the Adjudication of Claims of Injury Due to Exposure to Ionizing Radiation." This report was prepared in response to a request from the Administrator of Veterans Affairs, Veterans Administration (VA) dated December 11, 1984.

The CIRRPC report offers recommendations on the use of the 1985 "Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables" that identifies those cancers considered to be "radiogenic diseases;" provides screening doses of radiation to the diseased organ below which radiation causality would be remote; and advocates using the NIH report in evaluating, along with other evidence, cases not eliminated by the screening procedure. In developing these recommendations, CIRRPC has relied heavily on the concepts and definitions in the Veterans Administration's proposed and final rules, published in the Federal Register on April 22, 1985 and August 25, 1985, respectively. These rules address the meaning of the terms "at least as likely as not," "no reasonable possibility" and the VA's "reasonable doubt policy," all of which were considered by the Science Panel as criteria to be satisfied in developing its recommendations.

In transmitting this CIRRPC/Science Panel report I emphasize the following important considerations in its use:

- The report was prepared by the CIRRPC Science Panel whose responsibility was to address the questions asked by the VA from a strictly scientific perspective, rather than to consider policy ramifications. Consequently, CIRRPC does not intend that the report be construed as any form of policy recommendation.

CIRRPC has established a separate subpanel, composed of representation from Federal agencies, to consider policy issues that might arise from using, in some manner, a probability of causation approach in adjudicating claims of radiation diseases. However, any results from this effort would not affect the scientific content or the recommendations of the Science Panel's report.

- The screening doses set forth in the report are deliberately conservative in order to assure that any veteran's claim which has even a remote chance of being meritorious is considered. This conservatism is in part taken into account by specifying three credibility levels that surround the uncertainties in deriving these screening doses. However, the choice between these levels or the selection of higher or lower credibility levels is left to the Veterans Administration.

- The doses associated with a 50 percent probability of causation are provided in the report for information purposes only. The Science Panel does not mean to imply by this inclusion that compensation should be paid at this or any other particular level. Rather, each claim which passes the screening dose level should be considered on its individual merits.

- The report is based upon the "Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables," published January 1985. As the information in the NIH report may be updated and the values in the Tables revised to reflect new scientific information, the recommendations on the use of the NIH report and the derived screening doses in the CIRRPC Science Panel Report may need to be revised.

I believe the report is an important scientific contribution to the issue of compensation for those veterans with claims of service-related radiogenic cancer and I trust you will find its recommendations helpful.

Sincerely,

Alvin L. Young

Alvin L. Young, Ph.D.
Chairman, CIRRPC

COMMITTEE ON INTERAGENCY RADIATION RESEARCH
AND POLICY COORDINATION
1019 Nineteenth Street, NW, Suite 700
Washington, D.C. 20036

January 15, 1988

MEMO TO: Dr. Alvin L. Young, Chairman, CIRRPC

FROM: Dr. Randall S. Caswell, Chairman, Science Panel
Randall S. Caswell

SUBJECT: Science Panel Report entitled "The Use of Probability of Causation by the Veterans Administration in the Adjudication of Claims of Injury Due to Exposure to Ionizing Radiation"

I am pleased to transmit the Science Panel's report entitled "The Use of Probability of Causation by the Veterans Administration in the Adjudication of Claims of Injury Due to Exposure to Ionizing Radiation."

The report was prepared in response to a request from the Administrator of Veterans Affairs, Veterans Administration (VA) for the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) to provide guidelines to the VA with respect to the questions "...for what levels of radiation exposure, if any, the radioepidemiological tables can be used credibly in the rule-making we are conducting pursuant to Public Law 98-542" and "...whether CIRRPC's views in this regard vary with the type of cancer involved and whether use of the NIH tables for certain cancers may be more justifiable than for other cancers." The report prepared by the Science Subpanel on Radioepidemiological Tables and approved by the CIRRPC Science Panel answers these questions by listing those cancers both considered to be radiogenic in the NIH Report and to be applicable to veterans and by providing, for these cancers, radiation doses that allow the VA to exclude from further consideration those claims having "no reasonable possibility " (a VA stated criteria) of merit. Further, the Science Panel considers the NIH Report to provide important scientific information which can be used as part of the evidence for evaluating, along with other evidence, claims not eliminated by the screening procedure.

On behalf of the Science Panel, I take this opportunity to commend the Science Subpanel on Radioepidemiological Tables on its development of this report. It is well-written, creative and is a credit to CIRRPC's dedication to be responsive in meeting the needs of Federal agencies with "good science."

Enclosure

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## List of Tables

# USE OF PROBABILITY OF CAUSATION BY THE VETERANS ADMINISTRATION IN THE ADJUDICATION OF CLAIMS OF INJURY DUE TO EXPOSURE TO IONIZING RADIATION

## I. EXECUTIVE SUMMARY

In February 1985, the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) accepted, with the approval of CIRRPC, a charge to provide guidelines to the Veterans Administration (VA) with respect to the questions "...for what levels of radiation exposure, if any, the radioepidemiological tables can be used credibly in the rule-making we are conducting pursuant to Public Law 98-542 [Veterans' Dioxin and Radiation Exposure Compensation Standards Act]" and "...whether CIRRPC's views in this regard vary with the type of cancer involved and whether use of the [National Institutes of Health (NIH)] tables for certain cancers may be more justifiable than for other cancers." Subsequently, in April 1985 and in August 1985 the VA published proposed and final rules, respectively, to implement this Act in the adjudication of claims of service-related radiogenic cancer, noting its request to CIRRPC for guidance.

Using terms described in the VA rules as decisional criteria, the Science Panel adopted as a statement of its task the following question:

> To what extent can the NIH Report be used credibly to assist in adjudicating a veteran's claim of radiation injury in a manner that satisfies the "no reasonable possibility" and the "at least as likely as not" criteria stated by the VA and that is consistent with the VA's "reasonable doubt policy" acting in the claimant's favor?

The VA rules specify that "reasonable doubt" means that which exists after considering all evidence of record, and an appropriate balancing of positive and negative evidence which does not satisfactorily prove or disprove the claim. The rules specify that when sound medical and scientific evidence supports the conclusion that it is "at least as likely as not" that the veteran's disease resulted from exposure to radiation in service the claim can be adjudicated as meritorious. The term "no reasonable possibility" is not explicitly defined in the VA rules. However, the term is given meaning by the Science Panel by quantifying the likelihood that a specified "probability of causation" (PC) value in the NIH Report would not be exceeded, with an *a priori* chosen level of confidence.

At the onset, it is important to recognize the uncertainty that inevitably is associated with judgments of causation, whether such judgments are based on general

clinical experience or on relevant biological information. Nevertheless, the Science Panel finds the NIH Report useful in providing the following:

(i) a listing of radiogenic cancers applicable to claims of radiation-induced disease;

(ii) a probability-of-causation methodology upon which to base a screening test that for additional claim development involves only knowledge of the type of radiogenic cancer and the estimated radiation dose to the organ/tissue of interest; and

(iii) important scientific information which can be used as part of the evidence for further assessing causality in those claims which are not eliminated by the screening test.

The proposed screening procedure described herein was developed by considering the uncertainties surrounding a PC value of 50 percent (selected *a priori* to meet the decisional criterion of "at least as likely as not") to derive screening levels of radiation organ doses for each type of cancer considered in the NIH Report to be radiogenic and for exposure conditions applicable to veterans. Derived values are provided for different ages at exposure and for different credibility ("confidence") values chosen to meet the criterion of "no reasonable possibility." The Science Panel selected 20, 30, and 40 years as relevant age(s)-at-exposure and credibility values of 90, 95 and 99 percent. The screening procedure is biased toward ensuring that a marginal claim by an exposed veteran would not be rejected at this stage of consideration.

Claims not eliminated by this screening process would be adjudicated on their merit, taking into consideration the many factors that pertain to individual claimants, such as medical and personal information. Included in this consideration would be the "individualized" PC value based on the methodology described in the NIH Report. As the screening doses are biased to ensure consideration of even a marginal claim, use of the screening doses without this individualized claim review would be inconsistent with the Science Panel's recommendations.

The Science Panel proffers the following recommendations:

1. The NIH Report is directly applicable only to the following cancers listed as "radiogenic" diseases in the VA's final rules for adjudicating veterans' claims:

All forms of leukemia, except chronic lymphatic leukemia;
Colon cancer;
Esophageal cancer;
Female breast cancer;
Kidney cancer;
Liver cancer;
Lung cancer;
Pancreatic cancer;

Stomach cancer;
Thyroid cancer; and
Urinary bladder cancer.

2. For purposes of screening claims, Tables 1-3 in this Science Panel report may be used to deny causality for those claims which have "no reasonable possibility" of meeting the decisional criterion of "at least as likely as not." The selection of an appropriate credibility level to be used for applying this criterion is a choice left to the Veterans Administration.

3. The NIH Report[1] should be considered a scholarly and scientifically responsible document and accepted as a valid basis not only for the screening procedure developed, but also as a learned opinion of medical scientists in evaluating, along with other evidence, cases not eliminated by the screening procedure.

[1] The listing of radiogenic cancers and the calculation of organ screening doses are based on the January 1985 NIH Report. Review of new scientific information may warrant changes in not only the listing of cancers applicable to veterans but also the radiation organ doses associated with specific "probability of causation" values, including the screening dose levels presented in the Science Panel's Report.

## II. INTRODUCTION

### Request of the Veterans Administration

By letter dated December 11, 1984, the Administrator of Veterans Affairs, Veterans Administration (VA), requested the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) to provide guidelines to the VA with respect to the questions "...for what levels of radiation exposure, if any, the radioepidemiological tables can be used credibly in the rule-making we are conducting pursuant to Public Law 98-542" and "...whether CIRRPC's views in this regard vary with the type of cancer involved and whether use of the [National Institutes of Health (NIH)] tables for certain cancers may be more justifiable than for other cancers." The referenced radioepidemiological tables are those contained in the "Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables," published by the Office of the Director, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, January 4, 1985, NIH Publication No. 85-2748. This report is further referred to as the "NIH Report" and the scientists responsible for its development as the "NIH Working Group."

In February 1985, CIRRPC approved the effort to develop and provide the VA the requested guidance and charged its Science Panel to undertake development of such guidance. The Science Subpanel on Radioepidemiological Tables was given the responsibility to develop a draft report. Subpanel members and consultants are listed in Appendix A.

### VA's Rules for Adjudication of Claims

The Veterans' Dioxin and Radiation Exposure Compensation Standards Act (Public Law 98-542, October 24, 1984) required that the VA conduct rule-making regarding its guidelines for the adjudication of compensation claims which are based upon disabilities or deaths of certain veterans who, while in military service, were exposed to ionizing radiation. The stated purpose of the Act is to ensure compensation of

> ... Veterans who were exposed during service in the Armed Forces ...to ionizing radiation in connection with atmospheric nuclear tests or in connection with the American occupation of Hiroshima or Nagasaki, Japan, for all disabilities arising after that service that are connected, based on sound scientific and medical evidence, to such service.

The proposed rule to implement the Act (Federal Register 50:15848, April 22, 1985) noted the publication of the NIH Tables and the development of the concept of "probability of causation." Noting also the "many significant sources of uncertainty associated with the tables," as identified by the NIH Working Group, the VA did not adopt the use of the NIH Report in its proposed regulation, but rather sought guidance

from CIRRPC "in order to assess the potential utility of employing the tables in some fashion to adjudicate veterans' compensation claims." The final rule promulgated by the VA (Federal Register 50:34452, August 26, 1985) again noted its formal request to CIRRPC "to assess the utility of employing the tables in some fashion to adjudicate compensation claims."

## Definition of Terms

A number of important terms that relate to the adjudication of claims by the VA are defined or otherwise discussed in the aforementioned proposed and final rules. These terms were considered by the Science Panel to be decisional criteria which should be satisfied by any suggested use of the NIH Report and thus provided the necessary direction to the Science Panel's effort. In this context, they are discussed below.

1. "Reasonable Doubt" (38 CFR § 3.102)

The rule defines and applies the "reasonable doubt" policy in the following manner (emphasis added):

> When, after careful consideration of all procurable and assembled data, a reasonable doubt arises regarding service origin, the degree of disability, or any other point, such doubt will be resolved in favor of the claimant. By reasonable doubt is meant one which exists because of an approximate balance of positive and negative evidence which does not satisfactorily prove or disprove the claim. It is a substantial doubt and one within the range of probability as distinguished from pure speculation or remote possibility.

The Science Panel infers that any weighing of the positive and negative evidence is to occur after all the appropriate data have been assembled and not at each stage of the procurement of, or estimates made from, these data. Also inferred is that such weighing is performed using estimates derived from the data that represent "most likely" values and not "worst case" or "most conservative" values.

2. "At Least as Likely as Not"/"No Reasonable Possibility" (38 CFR § 3.311b)

The rule provides for a review by the VA's Chief Benefits Director and describes the conditions upon which to base a conclusion in the adjudication process. If, after evaluating specific factors that include probable dose, tissue radiosensitivity, sex, family history, age at exposure, time between exposure and onset of the disease, and exposure to other carcinogens (including radiation exposure received outside of service), "sound scientific and medical evidence" supports the conclusion that it is "at least as likely as not" that the veteran's disease resulted from exposure to radiation in service, the claim is considered meritorious. On the other hand, if this evidence supports the conclusion that there is "no reasonable possibility" that the veteran's disease resulted

from radiation exposure in service, the claim is considered to be without merit. If the Director is unable to conclude whether it is "at least as likely as not," or there is "no reasonable possibility," that the veteran's disease resulted from radiation exposure in service, the Director is required to refer the matter to "consultants selected by the Chief Medical Director [VA] from outside the VA, upon the recommendation of the Director of the National Cancer Institute."

3. "Sound Scientific and Medical Evidence" (38 CFR § 3.311b)

The rule defines these terms as follows (emphasis added):

> Sound scientific evidence means observations, findings, or conclusions which are statistically and epidemiologically valid, are statistically significant, are capable of replication, and withstand peer review. Sound medical evidence means observations, findings, or conclusions which are consistent with current medical knowledge and are so reasonable and logical as to serve as the basis of management of a medical condition.

## Science Panel Task

Using the above understanding of these terms, the Science Panel adopted as a statement of its task the following question:

> To what extent can the NIH Report be used credibly to assist in adjudicating a veteran's claim of radiation injury in a manner that satisfies the "no reasonable possibility" and the "at least as likely as not" criteria stated by the VA and that is consistent with the VA's "reasonable doubt" policy acting in the claimant's favor?

## III. APPLICABLE RADIOGENIC DISEASES

Section 38CFR 3.311b of the VA's final rule specifies that, for purposes of dose assessment and review of claims based on exposure to ionizing radiation, "radiogenic disease" shall include only the following:

All forms of leukemia, except chronic lymphatic leukemia;
Bone cancer;
Colon cancer;
Esophageal cancer;
Female breast cancer;
Kidney cancer;
Liver cancer;
Lung cancer;
Multiple myeloma;
Pancreatic cancer;
Salivary gland cancer;
Skin cancer;
Stomach cancer;
Thyroid cancer; and
Urinary bladder cancer.

With respect to latency for these types of cancer, i.e. the elapsed time period between the date when the alleged radiation exposure occurred and the date when the clinical diagnosis of the cancer was made, the rule specifies that leukemia and bone cancer must become manifest within 30 years after exposure, whereas other forms of cancer listed must become manifest 5 years or more after exposure. This assumption of five years or longer for VA-listed radiogenic cancers, other than leukemia and bone cancer, is somewhat different from the assumption adopted by the NIH Working Group which used a smooth transition curve from an assumed zero excess risk for the first five years after exposure up to a constant value of relative excess risk after 10 years following exposure. However, this difference does not affect the VA's listing of radiogenic diseases, since under either assumption a minimum latency period of 5 years would be applicable.

Of the 15 radiogenic cancers listed by the VA, only 13 are also listed in the NIH Report; multiple myeloma and skin cancer are not listed by the NIH Working Group. The NIH Working Group considers multiple myeloma "to have uncertain status as a radiogenic tumor" and states that reported associations between multiple myeloma and exposure to ionizing radiation "provide no basis for quantitative risk estimates." Likewise, while recognizing that skin cancer is "well-established as an effect of exposure to ionizing radiation," the NIH Working Group considers this cancer not to be well-established at low doses and states that "there is no quantitative basis for risk estimates in the region of practical interest." Without this quantitative basis for risk estimates, the NIH Report is not directly applicable to the adjudication of veterans' claims for multiple myeloma or skin cancer.

Two of the radiogenic cancers listed by the VA are included in the NIH Report only under such conditions that they are not applicable to the needs of the VA. Although probability of causation values (PCs) for salivary gland cancer are provided in the NIH Report, these values are only given for radiation exposures that occur below the age of 15, a condition not applicable to Armed Forces veterans. Similarly, PCs are provided in the NIH Report for bone cancer, but these values were developed only for radiation doses received from internally deposited radium-224, a short-lived alpha particle emitter. Veterans would not be exposed to this radionuclide as a result of their service-related activities.

For these reasons, the Science Panel considers the NIH Report to be directly applicable only to the following eleven cancers listed as "radiogenic diseases" in the VA's final rule:

All forms of leukemia, except chronic lymphatic leukemia;
Colon cancer;
Esophageal cancer;
Female breast cancer;
Kidney cancer;
Liver cancer;
Lung cancer;
Pancreatic cancer;
Stomach cancer;
Thyroid cancer; and
Urinary bladder cancer.

# IV. PROBABILITY, CAUSATION, AND PROBABILITY OF CAUSATION [1]

## Introduction

The concept that a disease such as cancer arises from an event or a series of events in one or more of the biological subunits that constitute the human body, and therefore is amenable to identification of its "cause," underlies much of medical diagnostics. In the case of cancer, many possible causes have been identified or suggested. Most of these causes are based on experimental data, but some are based on epidemiologic findings of increased incidence of certain types of cancer in people exposed to a wide variety of agents, including those in the workplace, the home, or the general environment. Presumably, these agents bring about the above-mentioned causal events in some of those exposed, resulting in the occurrence of cancer. However, the medical diagnosis of cancer *per se* does not provide any information on its cause, nor does exposure to a carcinogenic agent necessarily result in the development of a cancer.

There are no specific types of cancer that are exclusively brought about by exposure to one particular "causative" agent or associated with a single factor such as ethnic background, although for some types of cancers the majority of cases may appear to be related to one particular agent (e.g., pleural mesothelioma resulting from exposure to certain types of asbestos). Analysis of medical findings cannot separate the "radiogenic" cases from those unrelated to radiation exposure; no "biological markers" have yet been identified that can unequivocally point to radiogenic cancers, as distinct from non-radiogenic cancers. An excess incidence of cancer is identifiable in a statistical sense only.

Cancer induction is a stochastic (i.e., random) process and, in the case of ionizing radiation, the initial event responsible for the eventual development of cancer could be a single cell event resulting from the interaction of charged particles with cellular constituents. These events are neither rare nor unique to radiation, and the vast majority of biological changes brought about by such interactions are repaired or non-consequential. However, by "chance," one of the cells affected by radiation may develop uncontrolled growth and manifest itself in a clinically detectable cancer, a process which may take considerable time following the initiating event. Of the trillions of cells affected by radiation exposure, including natural background radiation, it is not possible to predict which, if any, cell will develop into a cancerous growth. For the present, on the basis of the epidemiologic evidence, scientists can only estimate certain probabilities that characterize the "causation."

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[1] Portions of this section are based on a detailed discussion of these concepts prepared for, and provided to, the Subpanel on Radioepidemiological Tables by Dr. Peter G. Groër, Oak Ridge Associated Universities, in consultation with Professor I.J. Good, Virginia Polytechnic Institute and State University. The Subpanel members acknowledge with gratitude Dr. Groër's contribution to its understanding of the conceptual and scientific basis of "probability" and "causation" as used in this report.

## Probability

The intuitive concept of "probability" as a qualitative measure is very old. Words such as "luck," "chance," "perhaps," "likely," etc., have a long history of use; for example, Aristotle defined "the probable" as that "what usually happens." Quantitative applications of probability are of relatively recent origin and were first developed for the quantification of gambling and actuarial (life expectancy) "chances." Actuarial applications have provided an approach to estimating the probability that a given individual, A, will be subject to a certain event (e.g., death) in the course of a certain time period. This can be done by observing a large number of individuals of the same age, sex, etc. as individual A, and by setting A's chances of death equal to the fraction of individuals dying during the postulated period. Thereby, an average probability of dying for individuals like A is derived. This provides a base from which to examine characteristics in A which may differ from other individuals assumed to be like A. It is this comparative approach that is normally applied in determining risk probabilities for radiogenic cancer that are based on analysis of epidemiologic data.

Probabilities derived in this manner cannot be totally objective, however, since they must rely on subjective judgments concerning degrees of uncertainty surrounding the data used. Thus, in the NIH Report, considerations of these uncertainties in deriving probabilities represent the consensus of a group of experts brought together for the purpose of providing a "best estimate" of such probabilities for certain diseases. As a consequence, these probabilities can be considered as "benchmarks" that, by allowing a comparison of individual characteristics of a claimant against the average of the class to which he or she belongs, assist in the determination of the "most likely probability."

## Causation

In view of the impossibility of determining causality on the basis of medical judgment, and the inherently subjective nature of "probability," it becomes clear that the concept of "cause" is probabilistic and is subject to the same considerations of subjectivity and judgment.

The assessment of whether the specified cancer in an individual would not have occurred without the specifically identified radiation exposure, implies the determination of the degree to which the following conditions have been satisfied:

- the probability of cancer after an exposure to ionizing radiation is greater than the probability of cancer in the absence of the exposure; and

- there are no other exposures to identifiable carcinogenic agents, in addition to the radiation exposure, that would produce the same effect.

The first condition requires that the cancer in question is at least potentially radiogenic, a condition assumed to be satisfied when the cancer type in question is listed in the NIH Report. The second condition can only be satisfied through informed judgment based on employment and medical records or other relevant environmental information on exposures to other agents equally or more likely to have caused the cancer in question. In some cases, such as lung cancer in a smoking claimant, a quantitative adjustment for other agents can be made to satisfy this second condition. In most cases, however, the resolution of causation is likely to be based on a numerical probability of causation, estimated on the assumption that the radiation exposure of the claimant is a relevant carcinogenic factor, and on subjective adjustments based on individual characteristics of the claimant and other relevant causation factors.

## Probability of Causation

Given that a radiogenic cancer cannot be differentiated from a "spontaneously" occurring one, the probability of causation has to be estimated indirectly. This probability of causation (PC) is the "likelihood" that a diagnosed cancer has been "caused" by a given radiation exposure or dose. For the purposes of calculating this likelihood, the PC can be defined as the increased risk (or probability) of the specific cancer due to a specified radiation exposure (dose), where the increased risk is expressed as a fraction of the total risk of developing this cancer. The total risk includes both the risk due to radiation and the risk from other causes, known and unknown. That is, for a given cancer, the probability of causation can be written:

$$PC = \frac{\text{Risk due to radiation exposure}}{\text{Baseline risk} + \text{Risk due to radiation exposure}},$$

where the denominator is the total risk. A mathematically precise definition of the PC is given in Chapter IV of the NIH Report.

Determining this PC requires estimating both the excess risk due to radiation and the "baseline" risk, i.e., the risk from all other causes. Both estimates of risk will depend on the type of cancer, a variety of individual characteristics of the person who has developed cancer, and exposure conditions. The NIH Report, for example, takes into account the radiation dose and dose rate, age at exposure, sex, elapsed time following exposure, and (for lung cancer only) smoking history. Other radiation exposures and other confounding factors are not accounted for, primarily because data are not adequate to determine their impact on the estimated PC. Chapters II and III of the NIH Report provide a discussion of these several "other" factors and the manner in which they are thought to modify cancer risks.

## Uncertainties in Probability of Causation Tables

It is very important to recognize that the probabilities derived in the NIH Report are based on extensive data and that the assumptions made, though somewhat subjective, represent the best judgments of knowledgeable experts familiar with the derivations, interpretations, and uncertainties surrounding these available data. It is in the context of their expert knowledge that the NIH Working Group carefully considered uncertainties in a variety of variables that surround estimated PC values, including uncertainties in both estimates of baseline risk and estimates of radiation risk. These uncertainties are discussed in detail in Chapter VII of the NIH Report and are briefly described here.

### Baseline Risks

The baseline risks used for calculating PCs are the age and sex specific cancer rates from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. These data cover the period 1973-1981 for ten areas of the United States, comprising about 10 percent of the U.S. population. The SEER rates are considered to be reasonably representative of the United States as a whole. However, they cannot take into account all of the characteristics relevant to causation for a given individual, making application of baseline rates to individuals somewhat uncertain. For example, a specific individual may have been exposed to many carcinogenic agents known to be associated with the specific type of cancer of concern, or the individual may belong to an ethnic group or come from a geographical region with a particularly low (or high) rate for the cancer of interest. In most cases, data are not adequate to determine the manner in which such exposures and factors affect causation.

### Estimates of Radiation Risks

Estimates of radiation risks are based primarily on data from epidemiological studies of human populations exposed to radiation for medical or occupational reasons or to the nuclear bombings in Japan during World War II. The atomic bomb survivors in Hiroshima and Nagasaki have played a particularly important role in determining radiation risk estimates. Because data on populations exposed at low levels are not adequate for reliable estimation of risk, estimates are based primarily on the experience of persons who have received relatively large doses of radiation at relatively high dose rates. The method used to extrapolate from high to low doses and dose rates is one of the most important sources of uncertainty. In the NIH Report, PCs for thyroid and breast cancer are based on linear extrapolation, i.e., on strict proportionality between dose and effect. The PCs for other cancers are based on a linear-quadratic dose response function for extrapolation, and the risk estimates for low doses are less than they would have been if they had been based on a linear extrapolation. The choice of the linear-quadratic model was guided mainly by radiobiological input from experimental studies, but is consistent with human data.

Another source of uncertainty is statistical variation in the estimated risk coefficients. The calculation of PCs requires estimates of "risk coefficients," often expressed as the number of radiation-induced cancers (or excess cancers) per million person--year per unit of radiation dose (e.g., rad). Because the exposed study populations from which these estimates are derived are limited in size, the estimates of risk coefficients are subject to uncertainties related to statistical (i.e., chance) variation. Given the statistical character of these uncertainties, they are quantifiable using standard mathematical methodologies.

Possible errors in the estimated doses assigned to exposed study populations, such as the Japanese atomic bomb survivors, provide a third source of uncertainty. Generally, radiation doses to individual members in these populations could not be measured precisely and may be a significant source of uncertainty in deriving risk coefficients to be used in estimates of probability. Underestimates of doses would result in overestimation of these risk coefficients, while overestimation of doses would result in underestimates. These uncertainties are not related to any uncertainty that may be associated with the dose defined for an individual claimant. This type of uncertainty arises from limitations inherent in personnel dosimetry, including the estimation of organ doses based on monitoring and other methods used in health physics.

The risk of cancer associated with exposure to radiation may depend on age at exposure, the time elapsed between exposure and diagnosis, and sex. Available data are not always adequate to determine how these factors, alone or in combination, might influence the estimation of risk. Thus, it is necessary to make certain assumptions with regard to the manner in which risks depend on these factors. For example, for cancers other than leukemia, it is assumed that the ratio of radiation risks to baseline risks depends on age at exposure, but this ratio remains constant during the remaining life span even though the baseline risk generally increases as a population ages. The assumptions chosen by the NIH working group to handle these factors, which are described in detail in the NIH Report, are supported by available data, but alternative approaches cannot be ruled out with certainty.

Many veterans seeking compensation will have served in their late teens or early twenties. For most cancer types, the tables in the NIH Report provide PCs that are largest for persons exposed early in life and decrease as exposure occurs later in life. Although available data provide good support for a higher PC for those young at exposure, the exact magnitude of the age differential is uncertain. Because the estimates of risks used in deriving the NIH radioepidemiological tables are based on about thirty years of follow up for most of the populations studied, those exposed early in life are just now reaching the age when cancer is most likely to occur, according to baseline risks. Thus, the estimates of relative excess risk may be more uncertain for this group than for those exposed at older ages.

An important source of uncertainty involves the treatment of smoking in determining PCs for lung cancer. In general, smoking is a far more important risk factor for lung cancer than low-LET radiation, especially when the radiation dose is low. Smo-

kers have risks that are about 10 times those for non-smokers, while according to the NIH Report a dose of 10 rad would not increase the risk of lung cancer by more than a factor of 1.3. The exact manner in which radiation affects risks in smokers and non-smokers is difficult to determine from available epidemiological data. For low-LET radiation (i.e., gamma ray) exposure, PCs given in the NIH Report are based on data which support the assumption that risks due to smoking and risks due to radiation are independent or "additive." This means that the risk of lung cancer due to a given radiation exposure for a smoker will be a much smaller proportion of his total risk than will the risk due to that same exposure for a nonsmoker.

All of these sources of uncertainty are recognized in the NIH Report and have been considered in developing the PC methodology and determining the estimates of PC for the various types of cancers. While the methodology is general, estimates of the NIH Working Group are for the "average individual" having the characteristics of a group that can be defined by condition of sex, age at exposure, etc. and the uncertainties described in the NIH Report. For the claimant, however, individual characteristics and other relevant factors may increase or decrease not only the estimated PC value but also the uncertainties surrounding the PC value.

## V. A PROPOSED SCREENING PROCEDURE FOR CLAIMS

### Introduction

In this section, a procedure is described for screening claims of radiation-induced cancer. This procedure is designed to insure that cases which have even a small chance of a true PC, that is 0.5 (50 percent) or greater (i.e., that meet the "at least as likely as not" criterion), are developed for assessment of causality, yet will avoid detailed development of those cases for which there is virtually no chance that the true PC would be as large as 50 percent. The screening process is not a decision-making process that should result in automatic compensation.

The screening procedure both favors the claimant and allows for consideration of uncertainties. It intends to separate virtually certain, non-meritorious claims for causality (i.e., "those of pure speculation or remote possibility") from those that have some chance of being adjudicated as meritorious (i.e., are "within the range of possibility"). In the latter cases, additional scientific and medical evidence which is specific for the individual cases will need to be analyzed, and at that time reasonable doubt is taken into account for those claims in which it is approximately "as likely as not" that the cancer was caused by radiation exposure received during the time of the claimant's service.

It was noted in section IV that the estimated PCs provided in the NIH Report are subject to several sources of uncertainty. This means that for an individual case, the true PC will lie within a range of PCs that is reasonably consistent with the available evidence in the case. Therefore, although the PC given in the NIH Report may be less than 50 percent, the possibility that the true PC exceeds this percentage cannot be ruled out with certainty, as the upper end of the associated range of uncertainty may exceed 50 percent. However, if the PC calculated from the NIH Report is close to zero, then, even with a large degree of uncertainty, one can be reasonably certain that the true PC does not exceed 50 percent, i.e., that it does not satisfy the "at least as likely as not" criterion.

It is expected that the vast majority of potential claimants for Veterans Administration benefits will have received doses of less than 5 rad (0.05 Gy), and that most claimants will have received doses of less than 1 rad (0.01 Gy). In most cases, the PCs given by the NIH Report for doses of 1 rad (0.01 Gy) or less are less than one percent, while the PCs for doses of 5 rad (0.05 Gy) or less are usually less than five percent. Because the PCs for these exposures are so small, the derived screening procedure could help to limit greatly the number of cases needing detailed development for causality without jeopardizing claims with medical and radiation exposure records that merit evaluation.

In order to accomplish this objective, it is necessary to quantify the various uncertainties discussed in Chapter VII of the NIH Report. Some of these uncertainties can be quantified objectively from the available data, while others require a more

subjective evaluation. It is possible also to estimate the effect of these several uncertainties acting jointly on the calculated PC. With this approach, an upper limit can be derived for any given PC. The level of credibility in this upper limit can be specified with 90, 95, and 99 percent being common levels.

If all sources of uncertainty could be quantified in a rigorous statistical manner from available data, the interpretation of an upper limit of (for example) 95 percent would be that there is only a five percent chance that the observed data could have resulted if the PC were as large or larger than the stated upper limit. This is the usual interpretation associated with "confidence" limits. However, because some sources of uncertainty must be evaluated subjectively, the term "credibility" limit, a term which reflects a more subjective concept of probability, is used instead. For practical purposes, a 95-percent upper limit can be interpreted as meaning that there is only a five percent chance that the true PC exceeds this value.

For screening purposes, it is then possible to determine the dose (specific to the cancer type, age at exposure, etc.) such that the upper 95-percent (or other specified level) credibility limit for the PC associated with that dose will be no greater than 50 percent. These doses will be referred to as screening doses. For any dose less than the appropriate screening dose, it follows that there is less than a 5 percent chance that the true PC exceeds fifty percent. The determination of such screening doses forms the basis of this screening procedure.

## Determination of Screening Doses

The determination of screening doses requires the following three steps:

1. Quantifying uncertainties;
2. Combining these uncertainties to determine upper credibility limits for PCs; and
3. Determining the doses corresponding to a PC upper limit of 50 percent.

The methodology for determining these screening doses is described in Appendix B, which includes the derivation of a screening dose model to accomplish steps 2 and 3 above and an explanation of the mathematical treatment of uncertainties in the model. Also, an example is provided, showing the determination of the screening dose for stomach cancer given certain conditions.

In Tables 1-3, screening doses for the radiogenic cancers listed in Section III are given for three credibility levels, 90, 95, and 99 percent. Entries are shown for ages at exposure of 20, 30, and 40 years. Kidney and urinary bladder cancers are treated as urinary tract cancer. Radiation dose is expressed in rad and is the average absorbed dose received by the target organ or tissue.

## Application of the Screening Procedure

A claimant's dose is compared with the screening dose indicated in Tables 1-3 for the appropriate type of cancer and age at exposure. If the claimant's dose exceeds the screening dose the claim should receive further development of causality.

Linear interpolation can be used for ages at exposure intermediate to those given in the NIH Report. The screening doses given for exposure at age 20 can be used for those younger than age 20 at exposure. Likewise, the screening doses given for exposure at age 40 can be used for those over age 40 at exposure. Two sets of screening values are given for each type of leukemia shown, one to be used if the case occurred within 20 years of exposure and the other for 20 or more years. For other types of cancer, the screening doses apply to all cases occurring five or more years after exposure. For lung cancer, there are also two sets of values in order to account for differences in smoking histories. The first set of values should be used if the potential claimant is known to be a smoker, while the second set of values should be used if the claimant's smoking habits are unknown at the time of screening, or claimant is known to have stopped smoking 5 years or more prior to diagnosis, or claimant is known to be a nonsmoker.

The choice of credibility level is an administrative decision which resides within the responsibility of the VA. The VA could also select higher, lower or in-between credibility levels, but such a selection would require additional calculations. In practice, it seems very unlikely that claims excluded from consideration of causality based on the "90-percent screening doses," but allowed consideration based on the "99-percent screening doses," would be found meritorious after the individualized claims are fully evaluated.

Table 4 lists the doses required to yield a PC of 50 percent if the NIH Report is applied directly. The fact that these doses are much larger than the screening doses developed by the Science Panel reflects the conservative assumptions that have been made in developing the screening procedure to meet the intent of the VA's "reasonable doubt" policy.

The screening dose methodology has the following characteristics:

* It allows for the possibility that the claimant has a lower baseline rate than average, corresponding to the 10th percentile of male rates (except for female breast cancer) for all counties in the United States. That is, consideration of individual characteristics of the claimant is very unlikely to raise the PC for doses at screening levels to 50 percent or more.

* It allows for the possibility of future adjustments of PCs as a result of new dose estimates for the Japanese atomic bomb survivors. This source of uncertainty is treated in the same manner as in Chapter VII, Section O of the NIH Report.

* It allows for additional uncertainty from a variety of sources, including all sources considered in Section O of the NIH Report and discussed in Appendix B of this report. Given these allowances and an allowance for a lower baseline rate than average, even a claimant with a low baseline rate who fails to pass the screening criteria would have a less than 1 in 100 chance (if 99-percent credibility limits are used) that his true PC exceeds 50 percent. With 95-percent credibility limits the chance would be 1 in 20, while with 90-percent credibility limits the chance would be 1 in 10. For a claimant with the average baseline rate, the chance of the true PC exceeding 50 percent will be much less than these values.

The following examples, based on the 95-percent screening doses in Table 2, illustrate the application of the screening procedure.

**Example 1**: A male claimant alleges that he received a dose of 12 rad at age 20 and developed acute leukemia at age 30. The screening dose in this case is 1.8 rad. Since the claimant's dose exceeds 1.8 rad, his case would be further developed for causality. The calculated PC for this case is 34 percent. Thus, based on the NIH Report alone, his PC is not as large as 50 percent, and causality would not be established if the decisional criterion "as least as likely as not" is applied at this 50 percent level. It is possible, however, that evaluation of the details of this claim could provide reason to adjust the PC upward.

**Example 2**: A male claims he received a dose of 1.2 rad at age 25 and developed cancer of the stomach at age 50. The screening dose for stomach cancer is 10.8 rad for exposure at age 20 and 21.2 rad for exposure at age 30. Thus, the screening dose is 16.0 rad for age 25 based on linear interpolation. Therefore, using the screening conditions described, his claim would not be further developed for causality because his dose did not exceed the 16.0 rad. In this case the calculated PC from the NIH Report is 0.46 percent. From the NIH Radioepidemiological Tables a dose of 126.3 rad is required to yield a PC of 50 percent for 25 years of age at exposure. This dose of 126.3 rad can be derived by interpolation between ages 20 and 30 for doses shown in Table 4.

**Example 3**: Claimant alleges that he received a dose of 17 rad at age 25 and developed cancer of the stomach at age 50. Since this dose exceeds the screening dose of 16.0 rad, the claim, in this case, just passes the screening criteria for further development of the causality issue. Using the NIH Report, the calculated PC is 6.9 percent. A claim based on a 15 rad dose would not have passed the screening criteria for further development of causality.

Passing the screening criteria should not be equated with having established significant causality. A claim based on an exposure to radiation that just passes the screening criteria has only a very remote chance of resulting in a meritorious finding after further development of causality.

Suppose the claimant in Example 3 were able to demonstrate that he lived in a section of the country that had especially low stomach cancer rates. For stomach cancer, the 10th percentile of all U.S. counties is a factor of 1.9 lower than the average rate. As discussed in the NIH Report (pp. 51-52), it is not clear whether or not adjustment should be made for this reason. However, if it were, the new PC would be raised from 6.9 to 12 percent, still well below a PC of 50 percent. If an additional adjustment is made for revised dosimetry in Japan by the factor of 1.62 (suggested in the NIH Report) the claimant's PC would increase from 12 to 19 percent.

Thus, even if this claimant's PC were adjusted for a low baseline and for revised Japanese dosimetry, the PC is still well below 50 percent. This would be expected since the screening dose of 16.0 is far below the dose of 126 rad (interpolated for age 25, Table 4) needed to obtain a PC of 50 percent if the NIH Report is used directly.

## VI. ROLE OF THE PC TABLES IN ADJUDICATING INDIVIDUAL CASES

The NIH Report represents an extensive effort to utilize relevant scientific knowledge and data for the purpose of estimating risks due to radiation, and, in turn, estimating probabilities of causation for certain types of cancer. Since the report reflects a consensus of scientists with expertise in several relevant scientific fields, it is not unreasonable to view it as an opinion deserving greater weight than that of individual experts. In those cases warranting further development of causality, the NIH Report provides a reasonable basis for assessing the significance of the risk associated with a given radiation exposure to an individual with a specific cancer of the type treated in the Report. However, the scientists responsible for developing the NIH Report could not give detailed consideration to every possible individual situation that might arise. Thus, it is possible that in individual cases some modifications of the PCs provided by the NIH Report might be warranted. It is also important that use of the NIH Report does not exclude consideration of the specifics of each claimant's case, including the type of radiation involved.

Most of the uncertainties reflect limitations in available data for developing scientific understanding and, thus, cannot be overcome by some other system of assessing risks due to radiation. It is important to understand that most uncertainties are bidirectional, so that the PC can be overestimated as well as underestimated.

The NIH Report should be considered an important piece of evidence that can contribute to the VA's requirement to take into account "sound scientific and medical evidence" in the adjudication of those veterans' claims for compensation for diseases allegedly resulting from radiation exposure. Further use of the NIH Report in developing causality for those cases that exceed the appropriate screening doses would be harmonious with and supportive of the rules of the Veterans Administration in adjudicating claims of service connected radiogenic cancer.

## VII. RECOMMENDATIONS

In response to the request of the Veterans Administration (VA) to the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) for guidelines on using the National Institutes of Health's (NIH) report on radioepidemiological tables in the adjudication of veterans' claims of radiation injury, the Science Panel of CIRRPC proffers the following recommendations:

1. The NIH Report is directly applicable only to the following cancers listed as "radiogenic" diseases in the VA's final rules for adjudicating veterans' claims:

All forms of leukemia, except chronic lymphatic leukemia;
Colon cancer;
Esophageal cancer;
Female breast cancer;
Kidney cancer;
Liver cancer;
Lung cancer;
Pancreatic cancer;
Stomach cancer;
Thyroid cancer; and
Urinary bladder cancer.

2. For purposes of screening claims, Tables 1-3 in this Science Panel report may be used to deny causality for those claims which have "no reasonable possibility" of meeting the decisional criterion of "at least as likely as not." The selection of an appropriate credibility level (90%, 95%, or 99%) to be used for applying this criterion is a choice left to the Veterans Administration.

3. The NIH Report should be considered a scholarly and scientifically responsible document and accepted as a valid basis not only for the screening procedure developed, but also as a learned opinion of medical scientists in evaluating, along with other evidence, cases not eliminated by the screening procedure.

Table 1. Screening Doses (in rad) to the Affected Organ/Tissue Based on Upper 90-Percent Credibility Limit [1/]

| Type of Cancer | Age at Exposure | | |
|---|---|---|---|
| | <20 | 30 | >40 |
| Chronic granulocytic leukemia [2/] | | | |
| within 20 years of exposure | 1.8 | 2.6 | 2.8 |
| 20 or more years post-exposure | 5.3 | 6.3 | 11.7 |
| Acute leukemia [2/] | | | |
| within 20 years of exposure | 2.3 | 3.7 | 8.2 |
| 20 or more years post-exposure | 7.0 | 8.2 | 10.8 |
| Leukemia (excl. chronic lymphatic) | | | |
| within 20 years of exposure | 2.3 | 3.5 | 6.6 |
| 20 or more years post-exposure | 6.6 | 7.7 | 10.8 |
| Colon cancer | 32.0 | 59.1 | 98.9 |
| Esophageal cancer | 14.1 | 33.2 | 52.2 |
| Female breast cancer | 32.0 | 60.0 | 120.6 |
| Kidney and bladder cancer | 26.5 | 43.7 | 63.3 |
| Liver cancer | 2.1 | 6.9 | 16.5 |
| Lung cancer | | | |
| known smokers [3/] | 46.1 | 83.4 | 119.3 |
| others [4/] | 8.6 | 18.0 | 28.2 |
| Pancreatic cancer | 13.8 | 30.7 | 51.5 |
| Stomach cancer | 13.7 | 26.5 | 42.8 |
| Thyroid cancer | 6.0 | 13.0 | 15.4 |

1/ A claim should be further developed for causality if the claimant's organ/tissue dose exceeds the values given in the table. Screening doses between age 20 and 30 or between 30 and 40 should be obtained by linear interpolation. A claimant with a dose less than the screening dose would have less than a 10 percent chance of having a true PC exceeding 0.5 (50%).

2/ Dose to active bone marrow.

3/ Known to have been a regular smoker (10 or more cigarettes per day) within 5 years of diagnosis. Screening doses are calculated based on the assumption that the claimant is a member of the average U.S. population that includes smokers and nonsmokers.

4/ Claimant's smoking habits are unknown, or claimant is known to have stopped smoking 5 years or more prior to diagnosis, or claimant is known to be a nonsmoker. Screening doses are calculated based on the assumption that the claimant is a nonsmoker.

Table 2. Screening Doses (in rad) to the Affected Organ/Tissue Based On Upper 95-Percent Credibility Limit [1/]

| Type of Cancer | Age at Exposure | | |
|---|---|---|---|
| | <20 | 30 | >40 |
| Chronic granulocytic leukemia [2/] | | | |
| within 20 years of exposure | 1.4 | 2.0 | 2.2 |
| 20 or more years post-exposure | 4.2 | 5.0 | 9.3 |
| Acute leukemia [2/] | | | |
| within 20 years of exposure | 1.8 | 2.9 | 6.5 |
| 20 or more years post-exposure | 5.5 | 6.5 | 8.5 |
| Leukemia (excl. chronic lymphatic) | | | |
| within 20 years of exposure | 1.8 | 2.8 | 5.2 |
| 20 or more years post-exposure | 5.2 | 6.1 | 8.5 |
| Colon cancer | 25.9 | 48.6 | 82.7 |
| Esophageal cancer | 9.1 | 22.2 | 35.8 |
| Female breast cancer | 26.7 | 50.9 | 104.3 |
| Kidney and bladder cancer | 21.1 | 35.2 | 51.7 |
| Liver cancer | 1.6 | 5.4 | 12.9 |
| Lung cancer | | | |
| known smokers [3/] | 37.8 | 69.6 | 100.6 |
| others [4/] | 6.8 | 14.4 | 22.8 |
| Pancreatic cancer | 10.3 | 23.4 | 40.0 |
| Stomach cancer | 10.8 | 21.2 | 34.8 |
| Thyroid cancer | 4.9 | 10.7 | 12.7 |

1/ A claim should be further developed for causality if the claimant's organ/tissue dose exceeds the values given in the table. Screening doses between age 20 and 30 or between 30 and 40 should be obtained by linear interpolation. A claimant with a dose less than the screening dose would have less than a five percent chance of having a true PC exceeding 0.5 (50%).

2/ Dose to active bone marrow.

3/ Known to have been a regular smoker (10 or more cigarettes per day) within 5 years of diagnosis. Screening doses are calculated based on the assumption that the claimant is a member of the average U.S. population that includes smokers and nonsmokers.

4/ Claimant's smoking habits are unknown, or claimant is known to have stopped smoking 5 years or more prior to diagnosis, or claimant is known to be a nonsmoker. Screening doses are calculated based on the assumption that the claimant is a nonsmoker.

Table 3. Screening Doses (in rad) to the Affected Organ/Tissue Based on Upper 99-Percent Credibility Limit [1/]

| Type of Cancer | Age at Exposure | | |
|---|---|---|---|
| | <20 | 30 | >40 |
| Chronic granulocytic leukemia [2/] | | | |
| within 20 years of exposure | 0.9 | 1.3 | 1.4 |
| 20 or more years post-exposure | 2.7 | 3.2 | 5.9 |
| Acute leukemia [2/] | | | |
| within 20 years of exposure | 1.1 | 1.8 | 4.1 |
| 20 or more years post-exposure | 3.5 | 4.1 | 5.5 |
| Leukemia (excl. chronic lymphatic) | | | |
| within 20 years of exposure | 1.1 | 1.7 | 3.3 |
| 20 or more years post-exposure | 3.3 | 3.9 | 5.5 |
| Colon cancer | 17.0 | 33.1 | 58.1 |
| Esophageal cancer | 3.9 | 9.9 | 16.7 |
| Female breast cancer | 18.8 | 37.0 | 78.6 |
| Kidney and bladder cancer | 13.4 | 23.1 | 34.7 |
| Liver cancer | 1.0 | 3.3 | 8.2 |
| Lung cancer | | | |
| known smokers [3/] | 25.5 | 48.8 | 72.1 |
| others [4/] | 4.3 | 9.3 | 15.0 |
| Pancreatic cancer | 5.8 | 13.7 | 24.3 |
| Stomach cancer | 6.9 | 13.8 | 23.2 |
| Thyroid cancer | 3.3 | 7.4 | 8.8 |

1/ A claim should be further developed for causality if the claimant's organ/tissue dose exceeds the values given in the table. Screening doses between age 20 and 30 or between 30 and 40 should be obtained by linear interpolation. A claimant with a dose less than the screening dose would have less than a one percent chance of having a true PC exceeding 0.5 (50%).

2/ Dose to active bone marrow.

3/ Known to have been a regular smoker (10 or more cigarettes per day) within 5 years of diagnosis. Screening doses are calculated based on the assumption that the claimant is a member of the average U.S. population that includes smokers and nonsmokers.

4/ Claimant's smoking habits are unknown, or claimant is known to have stopped smoking 5 years or more prior to diagnosis, or claimant is known to be a nonsmoker. Screening doses are calculated based on the assumption that the claimant is a nonsmoker.

Table 4. Organ/Tissue Doses (in rad) Corresponding to a PC of 50 Percent Based on the NIH Radioepidemiological Tables

| Type of Cancer | Age at Exposure | | |
|---|---|---|---|
| | <20 | 30 | >40 |
| Chronic granulocytic leukemia | | | |
| peak time of risk | 11.5 | 16.0 | 17.6 |
| 15 years post-exposure | 30.8 | 35.7 | 59.4 |
| Acute leukemia | | | |
| peak time of risk | 14.7 | 22.4 | 44.5 |
| 15 years post-exposure | 38.7 | 44.5 | 55.6 |
| Leukemia (excl. chronic lymphatic) | | | |
| peak time of risk | 14.4 | 21.4 | 37.1 |
| 15 years post-exposure | 37.1 | 42.4 | 56.6 |
| Colon cancer | 209.4 | 331.8 | 497.4 |
| Esophageal cancer | 183.8 | 331.8 | 458.6 |
| Female breast cancer | 92.3 | 157.0 | 287.3 |
| Kidney and bladder cancer | 258.1 | 368.3 | 483.5 |
| Liver cancer | 28.0 | 72.6 | 138.0 |
| Lung cancer | | | |
| smokers | 258.1 | 409.0 | 546.8 |
| nonsmokers | 73.2 | 128.0 | 178.6 |
| Pancreatic cancer | 112.4 | 202.2 | 297.9 |
| Stomach cancer | 95.6 | 157.0 | 225.9 |
| Thyroid cancer | 28.9 | 56.6 | 63.9 |

## APPENDIX A

## SCIENCE SUBPANEL ON RADIOEPIDEMIOLOGICAL TABLES

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# APPENDIX B[1]

## DETERMINATION OF SCREENING DOSES

### Derivation of Screening Dose Model

The PC is calculated as $R/(1+R)$ where R is the relative excess risk and is defined as the ratio of the risk due to radiation and the baseline risk. R can be written as the product of two factors, F(D) and G. F(D) is a function of dose (D) in rad and is taken to be $D+D^2/116$ in the NIH Report, except for breast and thyroid cancer following low LET radiation. Note that F(1) is approximately equal to one, so that G can be regarded as the relative excess risk for a one rad exposure and will sometimes be referred to in this manner.

For the purpose of evaluating uncertainties, G can be assumed to be the product of several factors G(i). G(1) is taken to be the overall risk coefficient (for a particular type of cancer), and the remaining G(i) indicate possible modifying effects of various factors as follows: G(2), baseline values; G(3), age at exposure; G(4), time response; G(5), dose-response relationship; and G(6), Japanese dosimetry.

$\hat{G}(i)$ denotes the estimate of G(i) that is used in the NIH report, and it is assumed (as in section O of Chapter VII of the NIH Report) that the $\hat{G}(i)$ follow independent lognormal distributions, with geometric means given by G(i)/B(i) and geometric standard deviations S(i), where B(i) denotes bias. Note that if $B(i)=1$, the uncertainty is unbiased, and that if B(i) is greater than one, then B(i) is the factor by which G(i) is underestimated. Specifically, the above model is based on the assumption that $\log \hat{G}(i)$ is normally distributed with mean ($\log G(i) - \log B(i)$) and standard deviation $\log S(i)$. [Note: log means the natural logarithm, i.e. $\log_e$.]

Since $\hat{G}(i)$ are assumed independent, an upper 95 percent credibility limit for $\log \hat{G}$ is given by

$$\sum_i [\log \hat{G}(i) + \log B(i)] + 1.645 * [\sum_i \log^2 S(i)]^{1/2}$$

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[1] This Appendix was prepared by Dr. Ethel S. Gilbert, Battelle, Pacific Northwest Laboratories, at the request of the Subpanel on Radioepidemiological Tables, in order to provide the scientific basis and mathematical methodology for the determination of screening doses. Minor editorial changes were made by the Subpanel which, however, did not affect the scientific content of the Appendix. It assumes familiarity with the NIH Report, particularly Chapter VII, Section O. The Appendix is intended for the reader who is interested in the technical details of the procedure used to determine screening doses.

and the upper 95-percent credibility limit, which will be denoted by R95, for $\hat{G}$ is given by

$$\{\prod_i B(i)*\hat{G}(i)\}*\exp\{1.645*[\sum_i \log^2 S(i)]^{1/2}\}$$

$$= \hat{G} * X95, \text{ where } X95 = \{\prod_i B(i)\}*\exp\{1.645*[\sum_i \log^2 S(i)]^{1/2}\} \quad (1).$$

More generally, to obtain a Z percent upper credibility limit, the upper Z percentile of a standard normal distribution would be substituted for 1.645.

Once the B(i) and S(i) are specified, the factor X95 can be calculated. $\hat{G}$ may be calculated as $PC_1/(1-PC_1)$ where $PC_1$ is the probability of causation given in the NIH Report for a one rad exposure.

The upper limit for G, the relative excess risk for a one rad (0.01 Sv) exposure, is given by $R95=\hat{G}*X95$ where R95 is the relative excess risk at the upper 95 percent credibility level. The upper limit for the relative excess risk for a dose D is given by R95 * F(D), and the corresponding upper limit for the PC for dose D is given by

$$R95 * F(D)/[1 + R95 * F(D)] \quad (2)$$

To calculate the dose corresponding to an upper credibility limit on the PC of 50 percent, the expression in (2) is set equal to 0.50, and solved for D. This leads to the following quadratic equation:

$$R95 * D^2/116 + R95 * D - 1 = 0$$

It remains to determine the specific B(i) and S(i) needed to evaluate the factor X95. This is done in the discussion that follows on evaluating sources of uncertainty with S(i) referred to as the GSD (geometric standard deviation), and B(i) as bias. The values of B(i) and S(i) used to determine the screening doses are presented in Table A.

Treatment of Uncertainties

a. Baseline Values

When the individual characteristics of a claimant are examined, it is possible that in some cases it will be determined that the person's baseline risk is different from the average, leading to possible adjustment of the PC. It is important that a screening procedure allow for this possibility.

If it is determined that an individual has been exposed to other substances associated with the type of cancer at issue, or if it is determined that the individual has a

family history of the cancer, the direction of the adjustment (if any) would be to raise the baseline risk and thus lower the PC from those given in the NIH Report. Potential adjustment in this direction is not of concern for screening purposes.

Consideration of the individual characteristics of a person could result in increasing the PCs given in the NIH Report only if the person could demonstrate that he or she were unusually free of exposures associated with the disease, or if the person demonstrated that rates from the area in which he or she had resided were substantially lower than the national average. (It was noted in the NIH Report that if the factors contributing to these differences act multiplicatively with radiation, the PCs as given in the NIH Tables are in fact appropriate, but in the interest of allowing the benefit of a doubt, it is possible one would want to adjust PCs based on such considerations.) To allow for this possibility, the proposed screening procedure is based on the assumption that the claimant has a baseline rate that is equal to the 10th percentile of male rates (except for female breast cancer) for all U.S. counties for the cancer type involved (Atlas 1975). That is, the screening PC is set sufficiently low that adjustment for a baseline risk that was at the 10th percentile of all counties would not yield a PC as great as 50 percent. It is unlikely that a person could make a solid case that his baseline was lower than this. The ratios of the average U.S. rate to the 10th percentile for several cancer types are given in Table A in the column headed B(2).

b. Age at Exposure

In the NIH Report, a geometric standard deviation (GSD) of 1.23 is used to reflect uncertainty resulting from age at exposure. This may not be adequate to reflect uncertainty in estimates of risk for those who are young at exposure. Much of the exposure of potential Veterans Administration claimants would have been received in their early 20's. For example, the overall GSD for all digestive cancer calculated from results presented by Land is 1.28 (Land 1986). By contrast, the GSD's for estimated age-specific coefficients are in the order of 2 or more. In order to increase the GSD of 1.28 to the level of 2, a GSD for age at exposure of about 1.9 is required. However, similar calculations based on breast cancer estimates presented in BEIR III suggest a GSD for age at exposure of 1.3.

As another means of assessing uncertainty, the ratios of the relative excess risks (from the NIH Report) for those exposed at age 20 and age 10 have been examined. This ratio is about 3 for lung and stomach cancer, but is somewhat smaller for acute leukemia, breast cancer, and thyroid cancer. Results for age 10 at exposure are not given for most cancer types.

In short, the uncertainty from this source is difficult to assess, and probably is not the same for all cancer sites. A GSD of 1.75 has been used allowing for a factor of 3 in the 95 percent two-sided credibility interval.

c. Time Response

For cancers other than leukemia, this uncertainty has been handled in the same manner as in the NIH Report (Chapter VII, Section O) with a GSD of 1.15. For leukemia, risk shows a wave-like response with a peak time at risk that depends on the type of leukemia and age at exposure. For the purposes of screening only, all cases occurring within 20 years of exposure are assumed to have the PC associated with this peak or maximum time of risk. For cases occurring more than 20 years after exposure, the PC associated with 15 years post-exposure is used. This approach may be unduly conservative, but leukemia is a sufficiently uncommon disease that it is unlikely to lead to large numbers of cases needing detailed consideration.

d. Dose Response Relationship

In the NIH Report, except for breast and thyroid cancer, linear risk coefficients derived mainly from BEIR III are multiplied by 0.4 to allow for reduced effectiveness of exposure when received at low doses and dose rates. There is uncertainty concerning whether there should be any reduction at all since a pure linear response cannot be ruled out based on epidemiological data. In preparing the tables of screening doses for various cancers (Tables 1-3, pp. 27-29), it has been assumed that the probability of linearity is 0.33 while the probability for the need for reduction is 0.67. A GSD of 1.43 is used for the uncertainty regarding the degree of reduction as in the NIH Report.

To apply these assumptions, two factors X95 are calculated as indicated in (1). For the first factor, X95A, B(5) is taken to be 2.5 and S(5) taken to be 1.0. For the second factor, X95B, B(5) is taken to be 1.0 and S(5) taken to be 1.43. X95 is then calculated as 0.33 * X95A + 0.67 * X95B.

e. Latent Period

For leukemia, this source of uncertainty is included by using the peak PC (as described above) for all leukemia cases occurring within 20 years of exposure. For cancers other than leukemia, the PCs associated with 10 or more years post-exposure are used for all cases occurring 5 or more years post-exposure. Thus, there is no need for including uncertainty from this source in calculating the overall GSD.

f. Japanese Dosimetry

Uncertainty resulting from the revision in the Japanese dosimetry is treated in the same manner as in Section O of the NIH Report where it is listed under "Risk Coefficient." However, unlike Section O, the correction has not been applied to breast cancer; in this case estimates have been verified in Caucasian populations. The treatment also differs from Section O in that the correction has been applied to liver

cancer. Even though data from thorotrast patients were considered in deriving PCs for liver cancer, with this data there is the additional uncertainty in extrapolating from high to low-LET radiation. Thus, the estimate for liver cancer is dependent on the Japanese data.

g. Risk Coefficients

Statistical uncertainty in the estimated coefficients was not included in the evaluation given in Chapter VII, Section O of the NIH Report. Since estimates for specific cancer types may involve considerable uncertainty, it is important to include this source of uncertainty in this Science Panel assessment. The estimate of the GSD requires the standard error of the logarithm of the estimate, which can be approximated by the standard error of the estimate divided by the estimate. The estimated GSD is then the exponential of this ratio.

As a rule, standard errors are not presented in the NIH Report, and it is difficult to trace the exact source of each estimate used and to determine its standard error. The sources indicated in Table B should provide a reasonably valid assessment of this source of error. With the exception of leukemia, uncertainty in the estimated relative biological effectiveness (RBE) of neutrons for estimates based on Japanese data was not included. To some extent, this source of uncertainty may be included in the uncertainty resulting from Japanese dosimetry, noted above; without consideration of RBE uncertainty, the GSD for leukemia would have been 1.05 (Kato and Schull 1982). Uncertainty in the separate estimates for different types of leukemia has not been considered.

## Screening Dose Example

CONDITIONS: 95-percent screening dose for stomach cancer, male, age at exposure is 20 years, time from exposure is 5 or more years.

The PC given in the NIH Report for a one rad (0.01 Sv) exposure for the situation in the example is 0.0057. Thus G, the estimated relative excess risk for a one rad exposure, is $0.0057/(1- 0.0057) \approx 0.0057$. The factors X95A and X95B (see above subsection d on dose response relationship) are calculated as follows:

$$X95A = 1.9*2.5*1.62*\exp\{1.645\ (\log^2 1.33+\log^2 1.75+\log^2 1.15+\log^2 1.17)^{1/2}\}$$
$$= 7.70 *\exp(1.645*0.6623) = 22.89$$

$$X95B = 1.9*1.62*\exp\{1.645(\log^2 1.33+\log^2 1.75+\log^2 1.15+\log^2 1.43+\log^2 1.17)^{1/2}\}$$
$$= 10.63$$

X95 is then given by $\{22.89 + 2(10.63)\}/ 3 = 14.72$

The upper limit for the relative excess risk G of a one rad (0.01 Sv) exposure is then given by 0.0057*14.72 = 0.084. The screening dose is determined by solving

$$\frac{0.084(D+D^2/116)}{1+0.084(D+D^2/116)} = 0.50.$$

The dose 10.8 rad (0.108 Sv) is found to satisfy this equation, and is the screening dose given in Table 2 for stomach cancer for exposure at age 20.

Table A. Bias, B(i), and Geometric Standard Deviations, S(i), used in Determining Screening Doses.

| Cancer Type | S(1) | B(2) | S(3) | S(4) | S(5) | B(5) | S(6) | B(6) |
|---|---|---|---|---|---|---|---|---|
| Female Breast | 1.15 | 1.9 | 1.75 | 1.15 | 1.00 | 1.0 | 1.00 | 1.00 |
| Colon | 1.33 | 2.4 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Esophagus | 3.14 | 2.3 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Leukemia | 1.31 | 1.2 | 1.75 | 1.00 | 1.43 | 2.5 | 1.17 | 1.62 |
| Liver | 1.28 | 2.6 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Lung | 1.28 | 2.2 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Pancreas | 1.83 | 1.9 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Stomach | 1.33 | 1.9 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |
| Thyroid | 1.08 | 2.7 | 1.75 | 1.15 | 1.00 | 1.0 | 1.00 | 1.00 |
| Urinary (kidney/bladder) | 1.43 | 4.1 | 1.75 | 1.15 | 1.43 | 2.5 | 1.17 | 1.62 |

S(1): GSD for statistical uncertainty in risk coefficient
B(2): Bias for baseline values (For screening purposes, it is assumed that all claimants have very low baseline risks)
S(3): GSD for age at exposure
S(4): GSD for time response
S(5): GSD for dose response relationship
B(5): Bias for dose response relationship

Note: S(5) and B(5) are not applied simultaneously, but rather as described in this Appendix, section "Treatment of Uncertainties," subsection d.

S(6): GSD for Japanese dosimetry
B(6): Bias for Japanese dosimetry

Table B. GSDs for Risk Coefficients for Each Cancer Type.

| Cancer Type | GSD | ----------Source of GSD---------- |
|---|---|---|
| Leukemia | 1.31 | BEIR III, p. 233, Table V-8 |
| Esophagus | 3.14 | A-Bomb survivor mortality data, Land 1986 |
| Stomach | 1.33 | A-bomb survivor mortality data, Land 1986 |
| Colon | 1.33 | A-bomb survivor mortality data, Land 1986 |
| Liver | 1.28 | Combined Hiroshima and Nagasaki tumor registries, NIH Report, p.218 |
| Pancreas | 1.83 | Combined Nagasaki tumor registry and British ankylosing spondylitis data, Land 1986 |
| Lung | 1.28 | A-bomb survivor mortality data, Kato and Schull 1982 |
| Urinary (kidney/bladder) | 1.43 | A-bomb survivor mortality data, Land 1986 |
| Female Breast | 1.15 | A-bomb survivor incidence data, Tokunaga et al. 1984 |
| Thyroid | 1.08 | Thymus irradiated patients, Shore 1980 |

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