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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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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-