Assigned Share for Radiation as a Cause of Cancer: Review of Radioepidemiologic Tables Assigning Probabilities of Causation: Final Report (1984)

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Review of Radioepidemiologic Tables Assigning Probabilities of Causation

Final Report
Oversight Committee on Radioepidemiologic Tables
Board on Radiation Effects Research
Commission on Life Sciences
National Research Council

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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PREFACE

On January 4, 1983, President Reagan signed into law the Orphan Drug Act, Public Law 97-414. Section 7(b) of the Act called on the Secretary of Health and Human Services to

> devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses.

The objective in developing such tables of "probability of causation" was to provide the scientific basis for an eventual formula for compensating cancer victims who claimed that ionizing radiation was the source of their cancers. The Act called for the tables to present the probabilities as "single percentage figure[s]" with a separate "evaluation which will assess the credibility, validity, and degree of certainty associated with [the] tables."

The Assistant Secretary for Health, through the Director of the National Institutes of Health (NIH), then established an Ad Hoc Working Group to Develop Radioepidemiological Tables centered in the NIH Intramural Research Program, but including representatives of other scientific and academic institutions. At the same time, he requested that a National Research Council committee be formed to "review the recommendations of the NIH Ad Hoc Working Group." This request was honored by formation of the Oversight Committee on Radioepidemiologic Tables in the Research Council's Commission on Life Sciences (with the cooperation of the Institute of Medicine).

The contract between the National Academy of Sciences and the NIH specified that the Oversight Committee should assess the utility of the data sources used by the Working Group for preparation of the radioepidemiologic tables, evaluate its assumptions concerning radiobiologic

effects, evaluate its epidemiologic and biostatistical methods, and evaluate the means by which it handled uncertainties. The Oversight Committee, in addition, chose to discuss in Chapter VII wider issues regarding the tables in the context of their intended and possible uses.

Because the Working Group wished to have an early review of its work, its chairman asked the Oversight Committee to comment on its assumptions and methods before it had completed work on the tables. The Working Group provided an informal draft report that discussed its preliminary conclusions, and the Oversight Committee submitted an interim report that reviewed that draft. After publication of the interim report, the Working Group revised its informal draft report to take account of some of the Committee's recommendations and then provided the Oversight Committee with a draft final report dated July 1984. This report is a review of that draft. In reaching the conclusions presented here, the Oversight Committee also reviewed earlier working papers prepared by the Working Group and other publications related to radiation effects and attributable risk. Throughout its review, the Oversight Committee had an open invitation to attend the meetings of the Working Group, and the members took frequent advantage of that invitation. J. E. Rall and his colleagues on the Working Group also provided information as needed. Without that information and cooperation, the work of the Oversight Committee would have been difficult, if not impossible.

The Oversight Committee recognizes that the task of creating and documenting the first set of tables of probability of causation is extremely difficult. The Working Group has done a great deal to advance the practical idea of probability of causation through its work and exposition, in spite of the many uncertainties, constraints, and controversial issues that it has had to face. The Oversight Committee recognizes the importance of these contributions of the Working Group and wishes to express its appreciation of that work, lest it be overlooked in the long critical discussions in this report.

The Working Group is already revising its draft final report; it may choose to modify it further after receipt of this final report. The Oversight Committee does not plan to review such modifications.

In reports of this kind, which must discuss a variety of charges to a committee, convenience suggests that each charge be discussed separately, and that is what has been done here. This approach leads almost inevitably to repetition of some ideas as they are treated from several points of view, often by different authors. The Oversight Committee has tried to minimize these redundancies.

We have also tried to aid the reader by indicating--at the point in the text where its discussion appears--the number of each recommendation given in the Executive Summary and--in the Executive Summary--the locations in the text where recommendations are discussed. Appendixes are also included for specific detail on selected aspects of this report and are placed apart so that the narrative of the main report reads smoothly.

This report, like the interim report, was reviewed by a panel of reviewers coordinated by Philip J. Landrigan. We thank them for their thoughtful and constructive comments; the report benefited greatly from their critiques.

The Oversight Committee is also grateful to its staff for expediting the production of this report. Stephen L. Brown was staff officer throughout the project, provided background material and early drafts of some chapters, and was responsible for repeatedly integrating the sometimes conflicting changes proposed by committee members and reviewers. Norman Grossblatt edited the manuscript, and Doris E. Taylor was secretary to the Committee for the final half of the project. Demissie Alemayehu performed some of the calculations. Other support was provided by Ramona Banks, Rebecca Bentz, Carolyn Gammon, Margaret Fulton, and Agnes Gaskin.

Finally, I want to thank Frederick C. Robbins and Alvin G. Lazen of the Commission on Life Sciences for their continued interest and support.

Frederick Mosteller
Chairman
December 1984

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CONTENTS

EXECUTIVE SUMMARY

Section 7(b) of the Orphan Drug Act, Public Law 97-414, directs the Secretary of Health and Human Services to develop radioepidemiologic tables that show the probabilities that human cancers are caused by prior doses of ionizing radiation. The Secretary delegated the responsibility to the Assistant Secretary for Health, who directed that the study be carried out by an Ad Hoc Working Group to Develop Radioepidemiological Tables, administered by the National Institutes of Health (NIH). The Assistant Secretary later asked that the National Research Council review the data sources, assumptions, methods, and means of handling uncertainty that the Working Group proposed. The Research Council formed the Oversight Committee on Radioepidemiologic Tables, which provided an interim report, covering an early draft of the Working Group's report, and a final report, covering the Working Group's draft final report dated July 1984. This document is the Oversight Committee's final report.

The conclusions and recommendations in this report will inevitably be compared with those in the Oversight Committee's interim report and those in the Working Group's final report. The result of an iterative process will be evident: the interim report influenced the Working Group's July draft, and this review of the July draft will influence the Working Group's final report. If this report achieves its purpose, some of its recommendations will no longer be relevant, because the Working Group will have adopted them in its final report.

The Oversight Committee originally thought that it would divide its recommendations into those reasonable for the Working Group to consider and those likely to be deferred to the future. On further thought, the Committee recognized that some recommendations would be relatively easy to accept, others would be possible but difficult to implement, yet others might require time and effort beyond the Working Group's current

scope, and some might require decades of scientific development for full realization. Rather than attempt such a detailed classification of recommendations, the Oversight Committee decided to present its findings and conclusions without any presumption about when or by whom they would be addressed.

The reader will note in the following that the Committee uses the term "assigned share" rather than the more familiar "probability of causation," for technical reasons explained in Chapter II. The latter is in some ways a misnomer, as we explain.

This executive summary first presents a chapter-by-chapter summary of the main text of the report and then lists the 25 specific recommendations that the Oversight Committee developed in response to its formal charge. The reader is referred to the main text for additional background information and details.

INTRODUCTION

If a person develops a cancer after being exposed to a dose of radiation, there is no known way to determine whether or to what extent the radiation influenced the development of the cancer. The lack of a clear cause-and-effect relationship poses difficulties for determining the validity of a claim for compensation for a cancer alleged to have been caused by radiation. Ordinary tort law normally makes an award if the evidence shows that the cancer more likely than not was caused by the radiation, and no award otherwise. In addition, that determination appears to be made inconsistently, and a compensation system based on "probability of causation" has been proposed as an alternative to tort-law proceedings.

Arriving at radioepidemiologic tables showing estimates of probability of causation or assigned share requires a body of epidemiologic and radiobiologic data and a series of assumptions and

methods for converting the basic data into probabilities of causation or assigned shares. These steps need to be outlined to guide further development of the tables and to allow independent verification and evaluation of the estimates in the current tables.

ASSIGNED SHARE (PROBABILITY OF CAUSATION)

It is possible to compute an assigned share or probability of causation for cancers that follow a specific dose of radiation by comparing two otherwise similar groups of people, exposed and not exposed. The value of the assigned share depends on the partition used for the computation and on the risk factors taken into account. The number of categories required is large; smoothing is required, and formulas or models must be chosen. The assigned share may be defined as the number of excess cancers in the exposed group divided by the total cancers in the exposed group. The Oversight Committee believes that the expression "assigned share" is more appropriate than "probability of causation," because the quantities being computed are not probabilities in the usual sense and are truly properties of the group to which a person belongs, but in practice are assigned to the person for purposes of compensation.

EPIDEMIOLOGY AND STATISTICS

In the past, the computational methods available to radiation epidemiology permitted only analyses by rather coarse categorization. It is now possible to take advantage of the fact that variations in risk with the size of risk factors should be smooth. Regression analyses of dose-response or time-response relationships can take all the data into account simultaneously, with such factors as age at diagnosis, age at exposure, and radiation dose incorporated into the models as either continuous or categorical variables.

The revision of the dosimetry in the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki could lead to substantial changes in radiation cancer risk coefficients, particularly with new techniques of analysis used on new cancer data available since the preparation of The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980, the "BEIR III" report. These changes could affect the present estimation of assigned shares in two ways: (1) a different method of projecting risks from Japanese to American cohorts might seem appropriate; and (2) the assigned shares could be changed by changes in dosimetry or by additional cancer incidence that is accumulating during followup (i.e., time since exposure).

To ensure reproducible estimates of assigned shares, algorithms and formulas should be used for assigning shares. Providing such algorithms and formulas is to be encouraged to avoid excessive tables and difficulties in determining an appropriate partition in what is really a spectrum of risks according to several continuous variables, including age at diagnosis, age at exposure, time since exposure, and dose.

The Working Group began with several assumptions regarding latency intervals, variation in risk with time after exposure, and the shapes of dose-response relationships. Several alternative statistical methods of analysis could be used--for example, starting with the raw data--rather than the analyses in the BEIR III report. Those methods allow departures from such assumptions as a fixed latency period or a prescribed form of hazard function and are commonly used in the analyses of quantitative data, for example, survival data.

No systematic appraisal of the designs and reliability of epidemiologic studies of dose-response relationships in radiation and cancer seems to be available. In some fields in the medical sciences, especially therapeutic trials, systematic studies of design, control, and statistical power have been most informative. A corresponding effort should be mounted for radioepidemiologic studies, particularly

for providing proper weighting of information for constructing tables of assigned shares.

ASSUMPTIONS

Developing radioepidemiologic tables from original data on baseline and radiation-related cancer risks requires assumptions about the variation of risk with time after exposure, with different population characteristics, and with several measures of exposure to radiation.

The Working Group selected wavelike time-response models for excess risk of leukemia and bone cancer, which are reasonable representations of the general form of the observed data, with some limitations. The Working Group has adopted a modified constant-relative-risk model for the time response of all other cancers. The Oversight Committee sees good support for this assumption in some data sets, but for others the available data from the Japanese experience might be more consistent with a constant-absolute-risk model. There is no scientific reason for the time response of any cancer necessarily to fit one of these models exactly.

The Working Group is not entirely clear on how to apply constant-relative-risk models to project cancer risk beyond 35 years after exposure. The available data do not resolve this issue, and there are some indications that the answers might vary according to the degree of exposure to other carcinogens, for example to tobacco smoke in the case of lung cancer and alpha radiation in miners.

Both age at exposure and cancer site influence the distribution of cancers over time after irradiation. The minimal latency interval is likely to depend on these variables; leukemias and bone cancers seem to have a shorter induction period than most other types of cancers. The Working Group has chosen an arbitrary method of smoothing that introduces stepwise discontinuities in estimates of risk. The Oversight Committee notes that the selection of minimal latency

intervals introduces perturbations, and a smoothing function that is continuous and that is dependent on age at exposure and on the specific type of cancer is required.

Two models concerning the interaction between cancer risk factors can be used to estimate excess risk in people who have both risk factors: the additive and multiplicative models. The Ad Hoc Working Group uses a multiplicative constant-relative-risk model for all cancer types other than leukemia and bone cancer, and for all risk factors other than smoking and those forming the partition. Smoking is assumed to act additively with low-LET radiation, but multiplicatively with high-LET radiation.

For low-LET radiation, the Working Group has adopted a linear-quadratic dose-response model for all cancers except thyroid and breast cancer, for which the response is assumed to be linear. The linear-quadratic assumption stems principally from selected observations in laboratory animals and cultured mammalian cells and from radiobiologic theory. Some scientists would prefer greater use of the linear hypothesis. On balance, the Oversight Committee welcomes the flexibility of the Working Group in allowing for more than one dose-response relationship, with the choice for a particular cancer type depending on available data.

The Oversight Committee finds the treatment of high-LET radiation, especially for internal sources such as inhaled radon and its decay products, incomplete. The Working Group was faced with the problem of estimating the risks of high-LET radiation without a substantial body of data in human populations. Radiation protection guidance for high-LET exposure has generally been developed by applying quality factors to the guidance for low-LET radiation exposure. However, use of these factors may be inappropriate for calculating assigned shares. Where possible, for example in uranium miners, direct estimates of the carcinogenic effect of high-LET radiation should be used.

The Working Group has proposed an adjustment for radiation protraction or fractionation that conforms with a linear dose-response model for any doses that extend beyond a 24-hour period. This approach seems reasonable under most conditions, but it should be better documented and could lead to discontinuities in assigned share for unusual dose delivery patterns.

DATA

The choice of a reliable compilation of baseline cancer incidence data applicable to the U.S. population as a whole may be limited to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The Oversight Committee sees no alternative to the decision of the Ad Hoc Working Group to use the SEER program for estimating baseline cancer rates, but it does recognize that the SEER data have limitations.

Each of the various reports and compilations of cancer risks from radiation appears to have limitations. None is sufficiently comprehensive or reliable to provide incidence data necessary for confidently estimating assigned shares, except under narrowly defined conditions. The Oversight Committee concludes that the BEIR III report has sufficient limitations to restrict its use in estimating assigned shares. In this regard, the risk coefficients in Table V-14 of the BEIR III report appear to require considerable revision and updating if they are to be satisfactory for estimating assigned shares.

One criterion for inclusion of specific cancer sites in the tables of assigned shares is sufficient evidence of a statistical excess in risk above the natural incidence. The Oversight Committee is, in general, in accord with the organ and tissue sites chosen by the Ad Hoc Working Group for estimation of assigned shares.

UNCERTAINTIES

The Orphan Drug Act directs the Secretary of Health and Human Services to evaluate the "credibility, validity and degree of certainty" of the radioepidemiologic tables. Uncertainties in the tables of assigned shares arise both from the data used to construct the tables and from the assumptions and methods needed to convert basic epidemiologic and radiobiologic data into assigned shares for radiation as a cause of cancer.

Even if the tables themselves were free of uncertainty, the information needed to use them for computing an assigned share for a cancer victim would still be uncertain. The dose received by the claimant and details of the radiation exposure will often be uncertain. The cancer diagnosis, smoking status, and existence of other risk factors may also be poorly known.

The Working Group discusses sources of uncertainty and presents a qualitative discussion of their magnitude and importance. However, it does not present much quantitative information about uncertainties and does not quantify their influence on the reliability of the assigned shares in the tables. The Oversight Committee recommends a quantitative appraisal of uncertainties, perhaps in the form of a sensitivity analysis, and has presented some examples of such analyses. Undoubtedly, the relative uncertainty in one assigned share may be very different from that in another. The Oversight Committee has found that the use of different reasonable assumptions or methods can produce estimates of assigned share that differ from one another by a factor of 4 or more when the Working Group's estimate is in the neighborhood of 20%. Considering all sources of uncertainty, the estimated assigned shares could often be substantially in error. As an example, the Oversight Committee performed a brief sensitivity analysis using the Japanese cancer data with a family of risk models different from that used by the Working Group. The results were seen to be sensitive to assumptions about the form of the model, about the

dependence of risk on age at diagnosis (or death), and about the variation in dose-response relationships with age at exposure.

WIDER ISSUES

The Oversight Committee decided to discuss some other issues that go beyond its formal charge, but that are likely to arise in applications of the tables of assigned shares. The Committee does not make formal recommendations on these matters that would be beyond its charge. However, the Committee does hold some opinions about these wider issues and has made statements regarding them. Each issue relates in some way to whether, when, and how the radioepidemiologic tables might be used.

Several circumstances might require that the tables of assigned shares change with time. One set of circumstances are actual changes in the factors that determine the values of assigned shares. For example, the appropriate baseline cancer rate for calculating assigned shares depends on the year of exposure and the year in which a specific cancer was diagnosed. These rates change with time, and provisions may be necessary to keep the tables current. Another set of circumstances entail improvements in our knowledge of the factors that enter the calculations. Our understanding of radiation-induced cancer will evolve as we acquire better dosimetry for exposed populations under study, accumulate more cancer data, develop better methods of analysis, and understand better the mechanisms of radiation carcinogenesis.

> It may be advisable to establish a standing committee to maintain a data base and improve the tables as time passes and knowledge accumulates.

As an integral or a separate activity, the NIH or another agency may wish to begin an appraisal of the validity and reliability of past epidemiologic studies on the role of radiation in human cancer and to develop and use improved epidemiologic methods.

The Oversight Committee recognizes that the current radioepidemiologic tables are uncertain. However, the potential exists for the uncertainties to be reduced. Specifically, the accuracy of the estimation of assigned shares can be improved by the current reassessment of the radiation dosimetry and cancer incidence in the Hiroshima and Nagasaki populations. As a result, many of the estimates in the tables could soon change markedly and seriously affect the amount of compensation that might be awarded a claimant. Such changes could cause confusion and might damage the credibility of the assigned-share concept and its application.

> The Oversight Committee believes that release of the current radioepidemiologic tables should be accompanied by explicit comment on their limitations.
>
> Furthermore, the Committee believes that a delay in mandating their application should be considered, until such uncertainties are substantially reduced by use of new data and methods.

If Congress decides not to delay implementation of the tables, then it would be important to have a clear plan for adjusting the treatment of compensation cases that were decided before the first major revision of the tables, such as that proposed in the Radiogenic Cancer Compensation Act, S. 921, pending.

The bill proposes to mandate the use of the tables in determining appropriate compensation, if any, for claims against the federal government involving cancer and radiation. The classes of claimants to be covered under the legislation are persons exposed to radioactive fallout from U.S. nuclear weapons tests, persons employed in uranium mines operated by the government, and service personnel participating in U.S. nuclear weapons tests. The current tables may have been constructed with these specific applications in mind. Other

applications are conceivable. One example would be claims involving occupational exposures to radiation in private industry. If the tables of assigned shares are applied to occupational exposures to radiation, they may have unexpected implications for radiation protection standards. The risk estimates used in estimating assigned shares may differ from those used in establishing the standards. Consistency in risk estimates between the organization that develops the tables and the ones that develop standards is desirable and should be encouraged.

Another example would be radiation received in connection with medical diagnosis or treatment. The Committee notes that medically exposed populations are different (sometimes greatly different) from the general population and that the values of assigned shares calculated for an unselected population would not generally apply to cancers--especially second cancers--in medically exposed persons. In addition, because medical radiation is used for therapy and diagnosis, compensation in these circumstances may be judged inappropriate for social reasons.

The pending legislation also proposes a specific formula for relating maximal compensation to estimates of assigned shares. The formula suggests that compensation be proportional to the assigned share value for assigned shares between 10% and 50%, that it not be awarded for assigned shares below 10%, and that it be full for assigned shares above 50%. These abrupt discontinuities exacerbate problems created by uncertainties in the assigned share tables. Slight changes in the tables can make major changes in the amount of compensation. Other formulas less sensitive to uncertainty could be considered. Several alternative compensation formulas are offered in Section VII D of this report.

The Oversight Committee notes the existence of precedents in such arenas as workman's compensation, where differences in medical costs, loss of income, loss of life, pain and suffering, and other factors are considered. The design of any compensation program based on assigned

shares would be improved by an appraisal of its benefits and costs in comparison with those of present or alternative systems under various assumptions about the classes of claims to be covered. Other comparisons with ordinary tort claims procedures would also be valuable.

RECOMMENDATIONS

The following recommendations are organized according to the four basic charges to the Committee: data sources, assumptions, methods, and uncertainties. They correspond roughly to Chapters V, IV, III, and VI, respectively, with considerable overlap. References are provided to sections of the report that explain the corresponding issues and provide the justification for our summary statements. (The chapters were ordered to present general ideas first and specifics afterwards; here the order is reversed, to emphasize the steps needed to estimate an assigned share.)

Data sources

1. The Oversight Committee recommends that the Working Group prominently indicate that the doses used in the tables are absorbed doses in organs and that use of other radiation measures, such as kerma or instrument readings, in calculating assigned shares will result in errors. (Section III D)

2. The Oversight Committee recommends that the Working Group consider other ways of defining the category of "leukemia excluding CLL" [chronic lymphocytic leukemia]--for example, ways that would exclude cases that should be diagnosed as CLL but are not. (Section VI D 1)

3. The Oversight Committee recommends that the decision of whether to include specific sites of cancer in the radioepidemiologic tables be based, to the extent possible, on an evaluation of the reliability of the estimates of assigned share, rather than on a subjective judgment preceding the data analysis. (Section V C)

4. The Oversight Committee recommends that, in compiling assigned shares in the future, greater use be made of original radio-epidemiologic data, including the latest updates available, and that correspondingly less use be made of derived risk coefficients, such as those from the BEIR III report. (Sections III A and V B)

5. The Oversight Committee recommends that the use of mortality data be considered for improving the understanding of the baseline incidence data and for identifying the uncertainties in the trends for those data. (Section V A)

Assumptions

6. The Oversight Committee recommends that the Working Group explain in greater detail the consequences of different time-projection models. Different models not only distribute observed cancer risks differently over the period of observation, but also lead to different estimates of risk for longer periods after exposure. The best choice of model is still uncertain, and the users of the tables should understand their limitations. (Section IV A 1)

7. The Oversight Committee recommends that the Working Group provide explicit guidance on projecting risks beyond the period of observed data--e.g., how to estimate an assigned share for a person whose cancer occurs more than 35 years after exposure--or else provide an explicit statement that it cannot now be done. (Section IV A 1)

8. The Oversight Committee recommends that full consideration be given to the possibility of reanalyzing the available statistics on excess cancer to model their time dependence without any specific assumptions about period of latency, rather than assuming a fixed minimal latent period and a prescribed form for the hazard function. (Sections III D and IV A 2)

9. The Oversight Committee recommends that, if analyses like those described in Recommendation 8 prove ineffective, consideration be given to allowing different minimal latency periods and different periods during which relative risks increase, for each specific type of cancer and age at exposure. (Section IV A 2)

10. The Oversight Committee recommends that the assumption of constant relative risks be reassessed as new data and new methods of analysis appear. (Section IV A 1)

11. The Oversight Committee recommends that the method for projecting relative risk estimates among populations be reconsidered when the tables are next revised. (Sections III A and IV A 3)

12. The Oversight Committee recommends that each revision of the tables include a fresh appraisal of the relationship between cancer risks and radiation dose and dose rate, allowing different responses under different conditions for different tumor types. (Sections IV B 2 and VI D 4) .

13. The Oversight Committee recommends that the Working Group further justify its decision on how to apply quality factors in calculating assigned shares for various high-LET radiations. (Section IV B 3)

14. The Oversight Committee recommends that a method for estimating assigned shares for persons exposed to high-LET radiation be developed that does not depend so heavily on the estimates for low-LET radiation. (Section IV B 3)

15. The Oversight Committee recommends that the current assumptions about the relationships between radiation and smoking be reviewed as new information on both low- and high-LET exposures accumulates. (Section III B)

16. The Oversight Committee recommends that the Working Group provide sufficient further documentation of its approach to handling dose rate for the calculations to be reproduced independently. Graphic displays showing the distribution of dose over time may be useful. (Section IV B 4)

17. The Oversight Committee recommends investigation of the possibility of modeling the response to radiation to include a variable for dose rate as well as dose, age at exposure, and age at diagnosis, with a smooth variation in response to changes in any variable. (Section IV B 4)

Methods

18. The Oversight Committee recommends that the Working Group discuss in detail the methods, data, assumptions, and calculations that need to be made to estimate assigned shares for radiation as a cause of cancer. Such a discussion would be useful to the users, as well as in the production of improved versions of the tables. (Section I C)

19. The Oversight Committee recommends that, before the Working Group disbands, it document completely the derivation of the factors used in the calculation of an assigned share. (Section III C)

20. The Oversight Committee recommends that a well-documented set of computer programs be developed to facilitate both tabulation of the factors used in the formulas and unambiguous application of the assigned-share formulas. (Section III C)

21. The Oversight Committee recommends that an alternative expression be considered for "probability of causation," such as "assigned share," that more accurately reflects what is being estimated. (Section II E)

22. The Oversight Committee recommends that the possibility of using a different partition of the population be kept in mind when new versions of the tables are being produced, to be consistent with relevant newly available information. (Section II C)

23. The Oversight Committee recommends that the available radio-epidemiologic data be analyzed with techniques that exploit the inherent smoothness of the relevant biologic processes. (Section III D)

Uncertainties

24. The Oversight Committee recommends that the Working Group conduct a quantitative appraisal, such as a sensitivity analysis, to evaluate the uncertainties in the assumptions, data, and methods used in constructing the tables; their influence on the reliability of the tables of assigned shares; and their implications for possible uses of the tables. (Section VI E)

25. The Oversight Committee recommends that the tables of assigned shares be updated promptly after the revised atomic-bomb dosimetry is released, with cancer data through 1982 or later if available and analysis with improved techniques if possible. (Section III A)

I

INTRODUCTION

A. Background

The understanding of radiation-induced cancer has increased steadily, if slowly, as information has accumulated in the human populations under study. Cancer risks associated with radiation are not easily quantified, especially among people who have received relatively low doses (under 50 rems or 0.5 Sv*) at low dose rates (measured in rems per week or year, rather than per second or minute). If a person who has experienced a dose of radiation later develops a cancer, it will be by no means clear that it was caused by the dose of radiation, because alternative explanations of cause will be possible. Furthermore, it is possible that the cancer was jointly caused by the dose of radiation and some other factor(s).

Today, when a cancer victim makes a claim of damage related to some specified dose of radiation, it may not be possible to judge the validity of the claim satisfactorily, except by arguing the case under ordinary tort law in a judicial or administrative tribunal. In such cases, awards of compensation are made, at least in principle, on the basis of the preponderance of the evidence. In statistical language, the judge or jury is asked to determine whether the probability that the radiation caused the cancer is less than or greater than 50% ("reasonable medical probability").

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* The National Council on Radiation Protection and Measurements has suggested retaining the older units of radiation exposure and dose, such as rads, but also providing the SI equivalents: 1 gray (Gy) = 100 rads; 1 sievert (Sv) = 100 rems.

Bond and others[9,10,33] have pointed out that fairness to both plaintiff and defendant might be improved if a systematic, reliable method could be used for determining a "probability of causation" to express the degree of association between the radiation dose and the observed cancer. In Chapter II, the term "assigned share" is suggested as a preferred alternative to "probability of causation," and "assigned share" is used in this report except where it might cause confusion. To illustrate the idea of assigned share, suppose 20 radiation-induced cancers occur in a group of 100 people with the same type of cancer, all of whom were equally exposed to radiation at the same time. Suppose further that each of the 100 people makes a claim for radiation injury, but that there is no way to identify which people have the radiation-related cancers. Presuming that the court were able to determine the number of radiation-induced cancers accurately, the assigned share would then be estimated as 20% for each member of the group, and none would be compensated by tort law. That decision seems unfair to plaintiffs whose cancers are truly related to radiation, but compensating all 100 of the plaintiffs at the full amount judged to be due a truly injured party seems unfair to the defendant.

Another problem is that some people believe that the courts have not handled well cases concerning compensation for cancer claimed to be due to radiation exposures and that the current adversary system involving expert witnesses and a jury does not augur well for justice in future settlements of such complex questions. The Oversight Committee knows of no critical examination of how well or poorly the current litigation process has worked.

For occupational injuries and illnesses, the tort-law system has been replaced in some cases by a nonadversary workman's-compensation system that bypasses the courts. A concern here, which is neither new nor restricted to radiation, is that workman's compensation does not work well in the case of cancer, where multiple causes are possible.

These perceived difficulties have stimulated increasing interest in devising a method by which the much-studied estimates of future risk in a population exposed to ionizing radiation can be converted to a quantitative estimate of the share to be assigned to prior radiation for a specific cancer in a particular person. Risk estimates are necessarily based on population studies, but the problems involved in compensation are different. The claimant in question has or has had cancer and is not merely at risk; furthermore, the dose received by the claimant has been estimated, and the question is whether the cancer is related to that dose of radiation.

As more is learned about radiation carcinogenesis, however slowly, the understanding of the influence of such factors as age, sex, genetic background, and exposure to other carcinogens on the risk estimates will also improve. Therefore, it seems both sensible and timely to examine methods of assessing, quantitatively, the relationship of specific cancers to prior exposure, knowing that the state of knowledge for the assessment will continue to improve.

Thus, the Oversight Committee welcomes attempts started by Bond[9] to examine and develop new approaches to the practical problem of compensation of persons with cancers that may be a result of exposure to radiation or some other carcinogenic agent.

In response to these issues, some members of Congress have proposed using "probability of causation" as the basis for compensation, with a formula to determine how much compensation should be offered, depending on the estimated probability or assigned share. They argue that, because a radiation-induced cancer cannot be confidently identified, every case of cancer in a homogeneous group of people equally exposed to radiation should receive the same compensation, presumably less than the full amount and possibly proportional to the assigned share. No such compensation scheme has yet been given official recognition in the United States, but Senate bill S. 921 of the Ninety-eighth Congress (the Radiogenic Cancer Compensation Act) proposes to use some method of

determining "probability of causation" for deciding whether the federal government should compensate some claimants with cancer. People who were exposed to fallout from nuclear weapons tests, employed by the government as uranium miners, or involved in nuclear weapons tests while in service and who later developed cancer are considered as potential claimants.

One of the schemes under consideration would establish an administrative compensation system, similar in concept to a Workman's Compensation plan, as an alternative to tort-law proceedings for claims against the government involving exposure to radiation. A nontort compensation system is much easier to create and defend when the cause-and-effect relationship is relatively clearcut in a person, as in the case of trauma or black lung disease, than when, as with radiation and cancer, it is highly uncertain for a given person. Recently, Karzon[36] proposed a scheme for compensating people with vaccine-related injuries: compensation by the federal government would be based on the frequency of occurrence and other considerations, no punitive awards would be made, and claims would be evaluated by an expert panel. The assigned shares for claims of this nature would likely be seen as near 100%, and a departure from the tort system would be comparatively easy. In another departure from the tort system, House of Representatives bill HR. 5400 would provide that patients treated under Medicare and Medicaid could be compensated for malpractice--or other claims usually covered under the Federal Tort Claims Act--via a compensation system that would set awards and eliminate further appeals. According to that bill, claimants would have to choose to use the administrative channel or to sue through existing tort law; they could not do both.

In preparation for the potential establishment of a probability-based compensation scheme, Congress passed Section 7(b) of the Orphan Drug Act, PL 97-414, calling on the Secretary of Health and Human Services to

devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses.

The Assistant Secretary for Health called on the Director of the National Institutes of Health to form an ad hoc working group to devise the tables and asked the National Academy of Sciences to form an oversight committee in the National Research Council to provide peer review of the products of the Working Group. The Oversight Committee prepared two reports: an interim report[51] covering the preliminary documents provided by the Ad Hoc Working Group on December 18, 1983,[1] and a final report covering the draft final report provided in July 1984.[2] This document is the Oversight Committee's final report. The Oversight Committee recognizes that the Working Group has already modified its July draft and may make additional changes in response to this report or to other critiques. Those modifications may cause some of our comments to become no longer applicable.

B. Charge to the Oversight Committee

The formal charge to the Oversight Committee had four parts:

o To assess the utility of the data sources used by the Working Group for preparation of the tables.

o To evaluate the Working Group's assumptions concerning radiobiologic effects.

o To evaluate the epidemiologic and biostatistical methods used by the Working Group.

o To evaluate the means by which the Working Group handled uncertainties.

The Oversight Committee decided, in addition, to discuss the tables in the context of their intended and possible uses (Chapter VII).

In the following chapters, the Oversight Committee addresses issues flowing from its charge. For each issue, the Committee identifies the nature of the issue, discusses alternative solutions, identifies the preferred alternative if one is clear, and--where appropriate--suggests how the choice made by the Ad Hoc Working Group might be modified. The Committee recognizes that the Working Group has proceeded under constraints of time, resources, available information, and practical considerations.

The Oversight Committee has inevitably traced the same path as the Working Group, if for no other reason than that members of the Committee have been privileged to participate in the discussions of the Working Group. Consequently, the material presented here, although independently assembled, to some extent overlaps the work of the Working Group. We tend not to spell out matters on which the Committee agrees with the Working Group, such as the basic list of issues. Instead, we emphasize matters that we think need more attention, or about which we currently prefer choices that do not match those of the Working Group. Neither the Oversight Committee nor the Working Group ordinarily speaks with a single voice. Joseph Berkson of the Mayo Clinic once remarked that, whenever a substantial body of intelligent people find themselves unanimous on a complicated issue, they should at once search for their common misapprehensions.

C. Radiation Measurements

Great care must be taken in specifying the measures of radiation that are associated with risks of cancer. Ideally, one would like to know the energy density deposited by radiation in the tissues where the tumor developed. This absorbed dose is measured in rads. The effects of the absorbed dose depend on its linear energy transfer (LET). For

low-LET radiation, the biologic dose equivalent of 1 rad is 1 rem, but for high-LET radiation, several rems may result from 1 rad.*

In principle, the Working Group expresses its risk and assigned-share estimates in terms of absorbed doses in tissue. However, with the exception of those to skin, tissue doses are rarely measured, but instead are estimated from external radiation information using factors related to body geometry.

The term "exposure" technically applies to the ionization produced in air by x rays or gamma rays only. Exposure is measured as the sum of all charges (of one sign) per unit mass of air and is expressed in roentgens. The energy of charged particles released when low-LET or high-LET radiation interacts with matter and which produces ionization is called kerma (kinetic energy released in material) and is also expressed per unit mass; its unit is the rad. Factors for converting from roentgens or kerma to absorbed doses in the body vary with type of radiation (high-LET or low-LET), energy spectrum of the radiation, and the geometry of the source of radiation and the tissue absorber.

Exposure and kerma can be calculated from the characteristics of the radiation source and of the attenuating material along the path of the radiation from source to point of exposure. Alternatively, they can be measured by properly calibrated instruments, such as film badges, dosimeters, or survey meters. Frequently measurements in a radiation field are expressed in rads kerma and refer to an unoccupied space rather than to the average dose to a specific organ or to the whole body.

This complicated situation invites errors in expressing either radiation dose information or coefficients for dose-dependent terms in cancer hazard functions. It is important fo recognize that absorbed

*In the SI system, the unit of absorbed dose is the gray and the unit of dose equivalent is the sievert.

doses in specific organs, needed for use with the radioepidemiologic tables, are not exposure or kerma values but are quantities, usually smaller if expressed in the same units, derived from those values by applying correction factors. Although the Working Group mentions the problem, the Oversight Committee feels that it deserves greater emphasis. In this report, we use the term "exposure" both as a general term to indicate that a person has received radiation and as a specific term to indicate the amount of radiation at a particular location in the air. We have attempted to restrict the term "dose" to absorbed dose in tissue, specifying where possible the specific tissue in question.

D. Steps in Estimating Assigned Shares

Were there a vast amount of epidemiologic data on cancer incidence rates for unexposed and exposed people in the United States under a variety of conditions, assigned shares for radiation might be estimated without simplifying assumptions. However, the available information is sparse, and much has arisen outside the United States, mostly in Japan. Using this information to estimate assigned shares for the U.S. population requires some assumptions. Ideally, each simplifying assumption would be justified by radiobiologic considerations, empirical results, or both. Table I-1 lists steps involved in the computation of an assigned share. This list could be elaborated by the Working Group in more detail and would be useful both for understanding how the current tables were constructed and for guiding the production of improved versions of the tables. (Recommendation 18)

TABLE I-1

Steps in Calculating Assigned Shares for Radiation

Specify and justify organ and tissue sites to be included in or excluded from the tables

Specify and justify assumptions about latent period

Specify and justify assumptions about the variation of excess risk with age (e.g., constant relative risk vs. constant absolute risk)

Specify and justify assumptions about excess risks in populations exposed to different risk factors (e.g., multiplicative risks vs. additive risks)

Specify and justify dose-response relationships (e.g., linear vs. linear-quadratic) and dose-rate assumptions

Specify and justify method of projecting risks across populations (e.g., from Japan to the United States)

Specify and justify sources of data and methods of estimating the coefficients of models

II

ASSIGNED SHARE: REFINING THE CONCEPT OF PROBABILITY OF CAUSATION

Some aspects of the notion of "probability of causation" are elusive, either because the definition is not clear or because approximations must be used. This discussion identifies and clarifies these concepts and proposes the term "assigned share" as an alternative to "probability of causation." Until we have justified such a change, however, we continue using the latter term. We begin by ignoring practical difficulties to get at fundamentals. For most types of cancer, we have no way to distinguish a cancer caused by a specified dose of radiation from one arising from some other cause. The probability of causation must relate to a specified exposure to radiation in connection with which a person is claiming injury. Although it over-simplifies matters, one idea behind probability of causation can be illustrated by supposing in a thought experiment that one can properly classify all cancers into either one group caused by the dose of radiation or another not related to that radiation.

A. The Ideal Situation: Known Causation

What does it mean to speak of the probability of causation for one person? That person has one cancer under discussion. If this cancer was "caused" by an identified dose of radiation, then the probability of causation by the dose is 1; if we find it "not caused" by the dose, then the probability is 0. Thus, for one person, we could classify perfectly, and only a 0 or a 1 would be assigned. When we come to groups, other probabilities may be assigned.

Let us move up a level from the individual to a well-defined group of people all having the same dose, say, U.S. men aged 30 at the time

of exposure and 50 at the time of diagnosis of a specific type of cancer. We continue to assume that each man's cancer is caused or not caused by the radiation. Suppose that, in 1,000 such men with a specific type of cancer, cancers of 200 men were caused by the radiation and cancers of 800 were not. We can compute the proportion of cancers of this type that are caused by the radiation, namely 200/1,000 = 0.2. This proportion is the probability of causation for this group; that means that, if a man is chosen at random from this group, the chance that his cancer was caused by the radiation is 0.2. The chance would be the same if we knew only that 200 cases were caused by radiation exposure, even if we did not know which men had those cancers.

B. The Importance of the Partition

We should note that if we change the population--say, from U.S. men to U.S. male smokers--then, even though we keep all else the same, the probability of causation might differ from 0.2, because a large fraction of the cancers may be caused by smoking. Let us suppose that the probability of causation by the dose of radiation in male smokers is 0.15. (The difference between 0.2 and 0.15 is not to be regarded here as due to sampling errors, but as a true difference.) Thus, the same man with the same type of cancer when regarded as a member of the U.S. male population might be associated with the probability of causation 0.2, but when identified with the U.S. male smoking population might be associated with 0.15. The point of the example is that, in general, "probability of causation" does not have any meaning until we describe a group for which we want an answer. Once that group is described, then a number becomes available through the kind of thought experiment we have just used. The same person might have a different probability of causation for each population he or she belongs to. All such probabilities of causation are valid if properly estimated, but they will differ numerically because they are based on different partitions.

More formally, if we can identify the cause (specific radiation exposure versus other cause) of a cancer for each member of a group, then the definition of probability of causation, PC, for that group is

$$PC = \frac{\text{number of cancer cases caused by the dose}}{\text{total number of cancer cases in the group}}$$

$$= \frac{\text{number of excess cancer cases in the group}}{\text{total number of cancer cases in the group}}. \qquad \text{(II-1)}$$

The second formulation, identical in meaning with the first, will help us relate and equate this definition to definitions introduced below. Note that the probability of causation applies to a group, and that we assign the same probability to each individual in the group. The word "assign" is important, because the everyday notion of cause used in the opening example no longer applies. Whether or not a person's cancer is truly caused by the radiation, he or she is assigned the same probability of causation. The fundamental step leading to unique probabilities of causation occurs when we divide a large population into mutually exclusive and exhaustive groups. For that division, a new individual will fall into one and only one of the groups and thus have only one probability of causation assigned.

The probability of causation assigned to an individual thus depends on the system used to divide the population. In statistics, this procedure is often called stratification. In this report, however, we will borrow from the language of probability and speak of forming a partition. A partition is a division of a population (in this case, of people) into mutually exclusive and exhaustive groups. The groups are called cells, strata, or categories. We define the partition by the variables, dimensions, or attributes used to divide the population. When we change the variables, we form a new partition. "Partition" refers to the rule for dividing the population or to the collection of categories produced; it does not refer to a single category or group.

Except for arithmetic accidents or special assumptions in the modeling, we expect individuals to receive different numerical values

of assigned probability of causation under different partitions. If a variable used in the partition is statistically independent of the other variables and of the source of the cancer, then its addition should not, in principle, change these values. In practice, fluctuations in the data ordinarily produce changes.

Without this awareness that the assigned probability of causation depends on the method of forming the partition, we are likely to have serious misunderstandings. Once practices are standardized, confusion is usually forgotten.

The Oversight Committee takes note of the discussion by the Working Group in Chapter IV A (pp. 66-67) of its draft final report. That summary may not convey this concept clearly and could give some readers the mistaken impression that PCs based on coarser partitions are not valid measures.

C. The Choice of the Partition

Who decides on the appropriateness of the partition? For life insurance and annuities, the covering company often decides, sometimes consulting with representatives of the group being insured. These partitions are usually decided in advance of the contract.

Sometimes society decides. For example, the Supreme Court recently decided for annuities that the partition that allowed women to be treated differently from men should be prohibited, even though men and women in 1984 have a difference in life expectancy of about 7 years.

For the probability-of-causation tables that the Working Group has constructed, the partition was initially ambiguous. Congress defined part of it by specifying that the tables take account of gender, age at exposure, age at diagnosis, size of dose, and type of cancer. After that, Congress gave leeway to the Secretary of Health and Human

Services, with the advice of experts, to use further subclassifications if desired.

Everyone can think of additional variables to use in the partition, such as smoking status, region of the country, rural or urban residence, occupation, and years of schooling. Although arguments can be made about fairness in connection with the choice of partition, and although science can in some instances tell the direction and magnitude of the effect of a change in the partition, the choice of partition is not only a scientific issue but a social and political one. This is underlined by the Supreme Court decision on gender and annuities. The courts might be asked ultimately to intervene and change the partition that was initially chosen for the radioepidemiologic tables.

The Working Group has chosen to add only the dimension of smoking status to those specified by Congress. Future versions of the tables may use a different partition, adding or deleting some dimensions, in response to the availability of relevant new information or because of directives from the Administration, Congress, or the courts. (Recommendation 22)

D. The Practical Situation: Unknown Causation

In practice, we cannot make the causal discriminations about cancer on a case-by-case basis as supposed in the introductory example. Therefore, we need a method for computing the probability of causation to be assigned. Suppose that we have two large populations that are equivalent in every respect, except that one population has been exposed to a given dose of radiation and the other has not. Suppose that, for a given age, 100 persons in the exposed group and 80 persons in the nonexposed group have a specific type of cancer. The excess cases of cancer associated with the radiation amount to 20 (100 - 80). Then the probability of causation, PC, is defined as follows:

$$PC = \frac{\text{total cancer cases in exposed group MINUS total cancer cases in nonexposed group}}{\text{total cancer cases in exposed group}} \quad . \quad \text{(II-2)}$$

This expression for probability of causation or assigned share is essentially equivalent to that presented as Equation II-1. In this example, we would compute the numerical value 20/100 = 0.2.

If the number of cancer cases in the nonexposed group turned out to be larger than that in the exposed group, then the radiation dose would be protective and produce a negative assigned share. For compensation purposes, we would force the assigned share to be zero. For present purposes, we are not considering sampling error, and it seems reasonable to replace negative values with zero.

E. The Assumption of Mutually Exclusive Causes

Until this point, we have taken the view that each cancer was either caused or not caused by a dose of radiation. That assumption of mutually exclusive causes is not required when the definition is based on the comparison of cancer rates in an exposed and an equivalent nonexposed population. In the latter approach, the excess cancers can be counted as related to the radiation without identifying the size of the contribution for a particular person. All that is necessary for computing the probability of causation through Equation II-2 is the numbers of excess cancers and total cancers in the exposed population. This PC no longer has a probabilistic interpretation in the sampling sense we used earlier, because some cancer cases are now "caused" by multiple causes, and we can no longer speak of the fraction of persons whose cancer was caused by the radiation dose. Even though the number computed is not a probability, it is a reasonable way to apportion blame for the excess, and so we think of it as a "share," rather than a probability. This share is assigned to every member of the group, and so we prefer the expression assigned share.

With this understanding of the concept of the probability of causation, it becomes possible to define the assigned share, AS, for radiation as one cause of cancer as

$$AS = \frac{\text{number of excess cancer cases in exposed group}}{\text{total cancer cases in exposed group}}. \qquad \text{(II-3)}$$

Notice that Equations II-1, II-2, and II-3 all have the same form; it is only the interpretation that differs. In the first equation, we assumed that we could identify the single causative agent for all the cancers in a group of people with cancer, and that the number of cases caused by the dose of radiation is the excess. In developing the second, we assumed that the cancers all have single causes and that we do not know which cancers have which causes. In the third, we saw that the second definition still applies even when the cancers do not have single causes. What is important here is the excess number of cancers, and so Equations II-2 and II-3 are really identical. Of course, this simple definition in words hides a host of complexities in practical application. The mathematical definition of assigned share is discussed in Appendix A.

To sum up, the expression "probability of causation" has several misleading features: the quantities calculated are not necessarily probabilities; the expression implies a simplistic view of causation--a single source of exclusive cause--that does not agree with the evidence; and it suggests that it applies to individuals, whereas in fact it is a property of a group that is assigned to all the people in the group. Despite these criticisms of the name, the Oversight Committee agrees that the formula (Equation II-2) is a valid interpretation of the intent of Section 7(b) of the Orphan Drug Act. The Committee prefers the expression "assigned share" and uses it in the remainder of this report, except where it might cause confusion.

The Oversight Committee recommends that an alternative expression be considered for "probability of causation," such as "assigned share," that more accurately reflects what is being estimated. (Recommendation 21)

F. Smoothing and Choice of Models

So far, we have spoken as though large quantities of data were available for a category in a partition, but of course that is not so. When the U.S. population is divided by sex, age at exposure, age at diagnosis, size of dose, and type of cancer, the number of categories is enormous. For example, if we assume that age at exposure and age at diagnosis are each divided into 50 yearly intervals, that dose is divided into unit doses between 1 and 100 rads (0.01 and 1 Gy), and that 10 types of cancer are induced by radiation, then we have $2 \times 50 \times 50 \times 100 \times 10$ or 5 million categories. Although this number can be reduced by grouping ages and doses more coarsely, the number of categories is usually large enough to make our straightforward approach of computing the probability of causation or assigned share impractical, because many categories contain few or no cases. Achieving suitable tables therefore requires some method of smoothing the data. Whether smoothing is to be guided by theory or by some other interpolation device, it is required whenever the data are sparse and the number of categories is large.

The choice of the method of smoothing can be guided to some extent by the available data, but the idea of a single "correct" method is misleading. Not all cancers seem to produce the same shape of the function that relates assigned share to dose of radiation. To create assigned shares that change smoothly with continuous variables--such as age at exposure, age at diagnosis, and size of dose--either a mathematical model or an algorithm for smoothing is required. Many models and algorithms are available. For the moment, the main point is that one must be chosen for each kind of cancer. Although it would be convenient if the same model could be used for all cancers, the

evidence shows that, among the model formulas commonly considered (e.g., linear, linear-quadratic, etc., for dose interpolation), different cancers may require different formulas. Furthermore, the choice among alternative formulas for a given type of cancer will ordinarily affect the resulting estimates in its table of assigned shares.

To go a step further, we rarely believe that the model is correct. Instead, we hope for a good approximation. Mathematics offers hope that polynomials of higher and higher degree will fit any smooth function more and more closely. Major advances sometimes come from noticing how observations depart from results of using a chosen model. Because the chosen formulas are not likely to be exactly correct, the tables might portray a biased result. What does this mean? Consider the assigned share generated for a particular dose for a person with specified properties. Suppose that we had extensive data on a group of such persons, so that we could determine the assigned share without making any special assumptions about the model. The bias in assigned share is then the amount by which the true assigned share for that group differs from the tabular entry computed from the model.

The use of a formula or an algorithm instead of tables makes it possible to treat each variable that enters the formula in detail, so that we can avoid class-interval issues. But it does not solve the problem raised by variables that are not included in the partition or the problem of the failure of the model to be strictly true.

G. Risk Factors Not Included in the Partition

A risk factor that is known to make a difference in the incidence of a specific cancer might not be included in the partition. Suppose, for example, that a claimant has a specific type of cancer that is thought to be associated with the extra risk factor. For example, the claimant might have leukemia and have some history of exposure to benzene. The defendant may argue that the assigned share for that

person should be lower, because the extra risk factor should be included in the partition. Many people will have identifiable risk factors that the tables and their adjustments do not handle directly. Congress or the courts will have to address the question of whether something should be done about these additional risk factors--or perhaps dismiss some risk factors that may now be included in the partition.

Beyond noting additional variables that might be included in a partition, we need to ask whether sufficient data are available to estimate an assigned share when those variables are used in the partition. In the benzene example, one would need to know how the risk of leukemia varied with radiation dose in the presence of various exposures to benzene.

H. Uses of the Radioepidemiologic Tables

Many ways of using the radioepidemiologic tables can be imagined. Three important, although simplified, ones are the following:

1. Direct use. The partition used in constructing the table determines an individual's assigned share, and that in turn determines compensation.

2. Starting-point use. The number in the table is used as a starting point for determining a new assigned share for the individual, on the basis of additional major facts--such as family genetics or time spent in various hazardous or nonhazardous occupations.

3. "Clinical" use. An attempt is made to estimate an assigned share for an individual, taking into account all his or her properties.

An operational definition of assigned share for the third use seems impossible with current knowledge, because for a specific person we

have no way to apportion blame to causes through verifiable measurements and outcomes in that person.

If one reads this whole report with its many uncertainties, one may also be pessimistic about the feasibility of the second approach. If the Working Group and the Oversight Committee have had trouble in deciding on the estimates to go into the tables, imagine the further difficulties that would be generated by adding variables without relevant data. Knowing how cancer rates vary in the whole population for different values of a new variable is not enough. We need to recompute the assigned share knowing how the rates vary with the new variable for each combination of values for the variables in the original partition. Large amounts of data or very strong assumptions will be required. In multivariate analysis, dealing with such conditional probabilities represents the rock on which inference so often stumbles. Once it is seen, the investigator casts about, searching for assumptions that would allow such inferences to be made. Plausible assumptions can sometimes be offered, but rarely with empirical evidence to support them.

Such assumptions can be seductive. Under some assumptions that might be used to construct tables of assigned shares, adding variables to the partition would not change the computed numbers, and this property may seem an attractive feature of the model. This advantage may then lead one to forget that the behavior of the model is probably not the behavior in the actual population, that evidence for either the assumption or the consequent property is weak or absent, and that the purpose of the partition is to make distinctions, not mask them.

The users of the tables should understand that an assigned share is no more the property of an individual than is a life expectancy; an individual will not usually live exactly as long as the life expectancy calculated for the group to which he or she belongs.

III

EPIDEMIOLOGIC AND STATISTICAL CONSIDERATIONS

This chapter discusses how the basic information on cancer incidence (or mortality) is analyzed to derive the relationships between risk and various measures of radiation exposure and how risk information is translated into assigned shares.

A. Epidemiology of Radiation-Induced Cancers

Epidemiology has demonstrated that increased risk of various specific cancers is related to radiation.[50] It has yet to quantify precisely the various relationships between radiation exposure and the probability of cancer.

The approach used in radioepidemiology has been to compare the incidence or mortality rates of a particular kind of cancer in one population or group with those in another, using two populations that differ in some measure of radiation exposure. The statistical significance of the difference between the two populations' cancer rates depends on the magnitude of the difference and on the numbers of cases and person-years of observation in the two populations. It is difficult to detect an association between radiation and cancer if the difference between rates is small, the number of people available for study is small, or the time between exposure and the appearance of cancer is short. Confidence is increased if several studies all point in the same direction.

Radioepidemiology has been hampered by difficulties in estimating radiation doses retrospectively or, in some instances, in verifying the fact of exposure. Imprecision in estimating radiation doses received by the persons studied results in uncertainty in the dose-response relationships determined. Particular difficulty is anticipated with

estimation of low-dose effects; the lower the dose, the greater the difficulty in estimating an effect. Consequently, the meaning of the studies can be interpreted differently by different investigators. As is discussed further in Chapter IV, a key point of contention is the way risk falls to zero as dose decreases, i.e., the shape or functional form of the dose-response relationship. Some epidemiologic studies show no excess cancer at doses below 50 or 100 rads (0.5 or 1.0 Gy) (see papers in Boice and Fraumeni[6]). But those studies are sometimes too small to have much chance of finding statistical significance even if a substantial excess is present, and some larger studies seem to demonstrate a significant increase after small doses.[29,58,62] Notable for its small doses (mean dose, 9 rads or 0.09 Gy) is the study of patients treated for tinea capitis with x rays[62] that showed statistically significant increases in thyroid cancer. A linear dose-response relationship significant at low doses was reported by Prentice et al.[52] in their study of thyroid cancer in Japanese atomic-bomb survivors.

When a population exposed to radiation is finely divided in the analysis with respect to age, sex, race, dose, dose rate, and so on and each category is analyzed separately, no statistically significant results can be expected to emerge. More sophisticated analysis is required, but it should not be assumed that radiation risk as a function of these variables cannot be well studied. The computational methods formerly available to radioepidemiology permitted analysis only by rather coarse categorization. It is now possible to take advantage of the fact that variations in risk with variations in the size of risk factors should be smooth. Regression analyses of dose response or time response can take all the data into account simultaneously, with such factors as age at diagnosis, age at exposure, and radiation dose incorporated into the models as either continuous or categorical variables. These matters are considered further later in this chapter.

Given the availability of such analytic methods, the Oversight Committee is concerned with the Ad Hoc Working Group's decision to

adhere largely to pre-existing risk estimates, especially those given in Table V-14 of the BEIR III report.[50] The Working Group recognizes many problems with this table, such as the nondependence on age of many of the estimates, especially for breast cancer. (See Chapter V for further discussion.) It therefore seems appropriate to reconsider all estimates in the light of the substantial body of evidence that has accumulated since BEIR III was completed in 1979.[6,72]

The Oversight Committee recommends that, in compiling assigned shares in the future, greater use be made of original radioepidemiologic data, including the latest updates available, and correspondingly less use be made of derived risk coefficients, such as those from the BEIR III report.' (Recommendation 4)

The Oversight Committee recognizes that other tables of "probability of causation" exist and are based on calculations that result in estimates substantially different from those used by the Working Group. As the Committee recommended in the interim report, the Working Group has listed such tabulations and has indicated briefly why they are not appropriate for the purposes of its task.

As discussed further in Chapter IV, the Working Group assumes that relative risks remain constant with time after exposure in each homogeneous population for many sites of cancer. It also assumes implicitly, in using the BEIR III risk coefficients, that the absolute excess risk over a period of observation is the same for populations in different geographic locations. These two assumptions may prove inconsistent. Appendix B discusses the statistical issues. The Working Group's justification for this approach is the similarity in excess (additional) risks for breast cancer in the Japanese atomic-bomb studies and two small epidemiologic studies in the United States. When using a constant-relative-risk model for each of two populations, projecting relative risks instead of absolute excess risks between these populations may be more appropriate.

The Oversight Committee therefore recommends that, when constructing improved versions of the tables, the responsible parties reconsider the method for projecting risk estimates among populations and reevaluate the possibility of using the same relative risk in every population category whenever they use a constant-relative-risk model. (Recommendation 11)

Because the dose estimates for the exposed people of Hiroshima and Nagasaki are undergoing major revision,[57] the estimates of the effects of radiation on induction of cancer could change substantially, once the updated dosimetry--as well as the accompanying new cancer data--is incorporated into new analyses of the atomic-bomb survivors. This new understanding could affect the estimated assigned shares in two important ways:

o A different method of projecting risks from Japanese to American cohorts might seem appropriate. This would affect one of the fundamental assumptions underlying the Working Group's approach.

o The assigned shares could be substantially changed by the changes in dosimetry alone, even if the underlying assumptions are not affected. They will also be changed by findings from the additional cancer incidence that is accumulating.

The Oversight Committee recommends that the tables of assigned shares be updated promptly after the revised atomic-bomb dosimetry is available, rather than waiting another 4 years. (Recommendation 25)

B. Other Risk Factors

Critical to the estimation of assigned shares to be applied to individuals in a group is an understanding of how radiation interacts with other risk factors. In the absence of radiation, "other" risk factors can be regarded--in the aggregate--as responsible for the increasing risk of most cancers with increasing age. Much available

evidence and underlying biologic theory suggests that the interaction between radiation and other risk factors may be multiplicative (in the context of a relative-risk model). The Oversight Committee notes (as did the Working Group) that, if an underlying multiplicative relationship between radiation and all other cancer risk factors is assumed, then consideration of smoking, genetic factors, or any other risk factor (other than sex, age at exposure, estimated radiation dose, and time since exposure) is not required in computing an assigned share. Thus, different tables--according to geographic area, race, smoking status, occupational exposure, etc.--are not required. However, if firm evidence shows that the interaction of radiation with a specific risk factor does not follow a simple multiplicative relationship, modification of the assigned shares may be required.

Questions have been raised on two factors: genetics and cigarette-smoking. The information available on the interaction of genetic factors with other carcinogenic processes, although scanty, is also compatible with a multiplicative relationship. The interaction of radiation with cigarette-smoking has been variously interpreted. Prentice et al.[53] could not determine whether a multiplicative or an additive relationship between cigarette-smoking and radiation in the induction of lung cancer represents a better fit to the Japanese data. Further evidence was derived by Whittemore and McMillan[74] from data in uranium miners; a multiplicative relationship seems to give a satisfactory fit. The Oversight Committee is concerned about the Working Group's interpretation that the relationship between radiation and smoking is additive for low-LET radiation. (Recommendation 15)

C. Presentation of Assigned Shares

The legislative mandate, Section 7(b) of the Orphan Drug Act, calls for "radioepidemiological tables" to present the information on the assigned shares ("probability of causation"). It further specifies that the information should be "displayed as a single percentage

figure" and should allow the user to determine the assigned shares "in terms of sex, age at time of exposure, [and] time from exposure to the onset of the cancer in question" for "any individual who has or has had a radiation-related cancer and has received any given dose." The range of doses specified in the act is 1 millirad to 1,000 rads (10^{-5} to 10 Gy); however, when President Reagan signed the bill, he noted the difficulty of establishing cause for low doses of radiation and directed that the tables be completed "to the extent that may be possible and scientifically responsible. . . ." Thus, although there is latitude to segregate the tables further and to choose the dimensions to be included on a single page, the Ad Hoc Working Group appears to have had a relatively narrow range of options for presentation of information. However, the Orphan Drug Act specifies that the tables must be accompanied by "a compilation of the formulas that yielded the probabilities of causation listed in the tables."

The Oversight Committee agrees with the Working Group that, to ensure reproducible estimates of assigned shares, algorithms and formulas constitute the basic mechanism for assigning shares. This method of portraying assigned shares is to be encouraged, to avoid a plethora of tables and to avoid difficulties in determining an appropriate partition in what is really a spectrum of risk according to several continuous variables--age at diagnosis, age at exposure, time since exposure, and dose.

The draft final report of the Working Group clearly presents the formulas needed to produce an estimate of assigned share from the claimant's dose and tabulated risk coefficients, baseline cancer rates, and factors describing the time dependence of risk. Reproduction of the tabular entries is more difficult, because the details of the required calculations are neither described explicitly nor illustrated graphically. For example, the conversion of the modified BEIR III risk coefficient, e, to the tabulated values of the relative-risk coefficient, $E(A_1,S)$, and the conversion of the Surveillance, Epidemiology, and End Results (SEER) data to the tabulated values of

the age-specific baseline cancer rate, $I(A_2,S)$, depend on a life table and an interpolation formula that are not presented. The documentation of the tables needs to be elaborated before the Working Group disbands, so that the entire process of deriving assigned shares can be independently reproduced and verified. (Recommendation 19)

The formulas actually used by the Working Group can be implemented by standard computer programs compatible with most modern small computers. What is needed is multiplication of the three terms provided in some detail by the Working Group; special computer programs are not required. However, the manipulations that produce the terms tabulated by the Working Group are much more complicated and will have to be updated or revised from time to time. The Committee recommends that a well-documented set of computer programs be developed, to facilitate both tabulation of the factors used in the formulas and unambiguous application of the formulas. (Recommendation 20)

D. Methods of Estimation

By definition, the assigned share (AS) at a given age, corresponding to a specified kind of cancer for a person of specified sex who received a specified total dose at a specified age, is

$$AS(t:d,t_0,s) = \frac{h(t:d,t_0,s) - h(t:d=0,t_0,s)}{h(t:d,t_0,s)}, \qquad \text{(III-1)}$$

where $h(t:d,t_0,s)$ is the incidence rate or hazard function (for example, new cases per year per 100,000 people) for diagnosis of this kind of cancer at age t for a person of sex s who was exposed to a specified single dose d at age t_0. The hazard function for unexposed people (d = 0) is the baseline cancer rate. Note that the dose estimated for an exposed person must match the dose for which the tables are constructed; the current tables appear to use absorbed doses in tissue, not the readings of film badges or kerma rads. The Working

Group should make it clearer to the reader which kind of radiation measure is used. (Recommendation 1)

The discussion of latent period in Chapter IV points out that a random time will elapse after exposure to radiation before a cancer grows large enough to be detected. Therefore, shortly after exposure, the excess risk from radiation will be near zero and the assigned share will be correspondingly small. The Working Group assumed, for all cancers except leukemia and bone cancer, that the risk is exactly zero for a period of 5 years after exposure and then increases by five steps over the next 5 years. The discontinuities are smaller than was the case with only one step, as was assumed in an earlier version of its report. It is more plausible that both hazard function and assigned share increase rather smoothly with time after exposure. The assigned share may later decrease when all the tumors resulting from the exposure have been detected.

Rather than assuming a fixed latent period and a prescribed form for the hazard function, the Oversight Committee suggests that available data might be used to evaluate a model and provide details. (Recommendation 8)

To learn how sensitive the outcome is to changes in the model adopted, additive, multiplicative, or other models could be tried, each with coefficients that change smoothly with time. This procedure is consistent with the biologic idea that the hazard function must be changing smoothly with small changes in dose, age, or time since exposure.

The Working Group, following the practices in previous risk-assessment efforts, such as BEIR III, decided to start with several special assumptions regarding the minimal latent period, the variation of risk with time since exposure, and the shapes of the dose-response relationships. Several other methods of analysis could have been used instead, starting with the raw data, rather than with the analyses in

BEIR III and elsewhere. Such methods allow the modifications alluded to above, as well as others, and are commonly used in the analysis of quantitative data (for example, survival data). The Working Group presumably considered using other methods and decided against them; it would be useful for the Working Group to state which major alternatives were considered.

One set of methods for survival data arise from the hazard-function regression model proposed by Cox.[16] Examples of this approach for radiation data were given in recent papers by Prentice et al.[53] and Whittemore and McMillan.[74] A somewhat different approach was taken by Brodsky et al.[11] Details are given in Appendix C.

As an example, consider leukemia and suppose that we use an additive model for the form of the hazard function, h. Brodsky et al.[11] assumed that

$$h(t:G,N,t_0,s) = a(t) + b_1(t)G + b_2(t)G^2 + c(t)N + d_1(t)t_0 + d_2(t)(G + N)s + d_3(t)(G + N)t_0 \qquad \text{(III-2)}$$

where $a(t)$, $b_1(t)$, $b_2(t)$, $c(t)$, $d_1(t)$, $d_2(t)$, and $d_3(t)$ are all age-dependent coefficients. (The subscripted d's should not be confused with the d used for dose in Equation III-1.) Brodsky et al. performed their analysis with two external measures of radiation--gamma radiation at kerma G and neutron radiation at kerma N--that may behave differently in the hazard function. In this example, the hazard function depends linearly on the neutron kerma, so the coefficient c(t) measures the effect of the neutron kerma for a person of sex* s who was of age t_0 at the time of exposure and also was exposed to gamma radiation. Thus, c(t) is the increase in hazard at time t corresponding to a unit increase in N under the specified conditions. Kerma G can produce a curvilinear dose-response relationship. The two

* For this formulation, s must be coded numerically.

interaction terms, $d_2(t)(G + N)s$ and $d_3(t)(G + N)t_0$, indicate that the sizes of the sex effect and the age effect may depend on the total kerma, G + N. Special cases of the general model include those which are linear in gamma kerma [$b_2(t) = 0$] or purely quadratic in gamma kerma [$b_1(t) = 0$]. Except in the interaction terms, where gamma kerma and neutron kerma are assumed to have equal effects, this formulation imposes no relationship between the effects of gamma radiation and neutron radiation that forces us to transform one into the other, so data from both Hiroshima and Nagasaki can be analyzed; that property is important, because the data are limited.

In the analysis used by Brodsky et al.,[11] some models fitted slightly better than others. Their data are not grouped; each person who was alive without cancer at the start of the interval is treated individually. That procedure tends to produce more reliable and efficient estimates when risks vary smoothly with age at exposure, etc.

We can carry out a similar procedure with a multiplicative model. Using Greek letters for coefficients because the individual effects are different from those of the additive model of Equation III-2, we can express a multiplicative model as a log-linear model:

$$\log_e h(t:G,N,t_0,s) = \alpha(t) + \beta_1(t)G + \beta_2(t)G^2 + \gamma(t)N + \ldots \quad \text{(III-3)}$$

The procedure used in the additive model is now applicable to this form. The estimated effect of neutron kerma, for example, is $\gamma e^{(t)N}$ in the presence of the other effects.

Because the observed rates are small, a logistic-linear model might also fit well. This model is linearized by taking the log of the odds ratio, that is,

$$\log_e \frac{h(t:G,N,t_0,s)}{1 - h(t:G,N,t_0,s)}.$$

This model has the advantage that it forces the estimated h to be between 0 and 1. The hazard function increases slowly at first, then more rapidly, and finally more slowly again. This functional form may be intuitively appealing. An analysis of selected mortality data from Hiroshima and Nagasaki using a variation of the methods described here is presented in Appendix D.

Instead of using raw data for individuals, the Working Group used formulas taken from BEIR III for almost all tumors. The derivation of those formulas involved computations performed with data grouped arbitrarily over dose, time, and age interval. It is informative to examine how the proportions of persons with cancer change with dose, age, and age at exposure for each sex, even though the samples are small and the sampling variability causes confusion. The estimates of risk derived from BEIR III vary irregularly with age at exposure and were smoothed through an arbitrary interpolation procedure to give risk coefficients for annual increments of age.

More flexible methods, such as described above, are more efficient and take advantage of the smoothness in risk that accompanies small changes in the explanatory variables. Modern computing facilities make general regression models with multiple terms and coefficients simple to evaluate, so there is no apparent advantage in grouping the data or in adapting simpler formulas from BEIR III. The computer programs used to evaluate the models also provide estimates of the precision of the estimates, in terms of standard errors for the coefficients. These estimates can be used to assess the reliability of the models.

One other method of analysis would arrange the data into a much finer contingency table (with little grouping) and then smooth the entries in the table by running averages or using some similar smoothing technique that takes advantage of the ordering of the categories (see Burman[12] for a summary). Such methods might also be more efficient and less biased than the method used by the Working Group. They differ from the Brodsky _et al._ method in that no explicit

form for hazard function need be assumed (except perhaps in the smoothing weights). However, the advantage of being able to interpolate and extrapolate the assigned share may be lost.

The Oversight Committee recommends that the data be analyzed with techniques that exploit the inherent smoothness of the biologic processes. (Recommendation 23)

For leukemia, the Working Group has used a time-response model that estimates the number of cases that might have occurred in Japan before the lifespan studies began. For all other cancers, its assumption regarding the minimal latent period would lead to the conclusion that the experience in the first 5 years after the bombs was of no consequence in the analysis. Some authors have speculated that the people who died in the first 5 years might have differed from those who survived in such a way as to complicate the analysis of radiation risks based only on the survivors. This difficulty provides an additional source of uncertainty.

Although Land[39] has discussed the difficulties of radioepidemiology, no complete systematic appraisal of the designs and the reliability of the epidemiologic studies of dose-response relationships in radiation and cancer seems to be available. In some fields of medicine--especially in therapeutic trials--systematic studies of design, control, and statistical power have been most informative, showing, for example, that observed size of effect depends heavily on design and degree of control,[14,15,17,22,25] that many studies have such low power that they could not reliably detect improvements as large as 50%,[23] and that the whole collection of studies in some fields is so weak that a revision of standards of investigation may be required.[60] Those experiences in an analogous situation suggest that a corresponding effort ought to be mounted in studies of the effects of radiation. Indeed, without such studies, we cannot know the proper weighting of information for such work as constructing the radioepidemiologic tables. NIH or another agency may wish to begin an

appraisal of the validity and reliability of past epidemiologic studies of the effect of radiation in human cancer and to develop and use improved epidemiologic methods.

E. Multiple Cancers and Multiple Radiation Exposures

We turn now to more complicated situations, some not covered directly in the tables of assigned share prepared by the Working Group.

What if a person has more than one kind of cancer--say, C_1 and C_2--both of which are primary cancers that followed radiation dose d at age t_0? The handling of such complications needs to be developed for future versions of the tables.

There may be instances in which a person who has received radiation from several sources wants to determine an assigned share for one of these sources. For example, someone might have received occupational radiation while working in a uranium mine and military radiation while in service at a nuclear weapon test. That person might want to determine the assigned share corresponding specifically to the occupational radiation. Suppose that d_o rads were from occupational sources and d_m rads were from military sources. Both doses will in general increase the risk of some types of cancer after the minimal latent period, and we wish to determine the assigned share corresponding to one of these (say, d_o), given that the person also received d_m rads from another source.

Suppose $E(d_o)$ and $E(d_m)$ denote the excess risks for doses d_o and d_m, respectively, given alone. The Working Group asserts that the total excess risk, $E(d_o,d_m)$, corresponding to dose $d_o + d_m$, satisfies

$$E(d_o,d_m) = E(d_o) + E(d_m). \qquad \text{(III-4)}$$

Using this formula, it computes a formula for the assigned share corresponding to dose d_o, given that the person also received a dose d_m. This formula assumes that the minimal latent period has elapsed for both doses of radiation.

It should be noted that Equation III-4 implies a linearity assumption about the dose-response function, which need not always hold. The assumption can be shown to hold (see Appendix E) whenever the risk corresponding to $d = d_0 + d_m$ satisfies

$$h(d) = h(0)(1 + \omega\ d), \qquad \text{(III-5)}$$

where h(d) is the risk at dose d, h(0) is the risk in the absence of radiation, and ω is a constant.

However, Equation III-5 does not hold when the risk corresponding to dose d is nonlinear in d (e.g., linear-quadratic). Consequently, the formula for computing an assigned share specific to dose d_o (when there is another dose d_m) does not directly apply for tumor types for which a model that is nonlinear in dose is used, unless the separation in time of d_o and d_m can be shown to make them independent. Equation III-4 also assumes that the cancer occurs long enough after the last dose for the minimal latent period to have elapsed.

It can also be verified (see Appendix E) that, when Equation III-5 does hold, the assigned share corresponding to dose d_o when $d_o + d_m$ rads was received can be obtained from the standard assigned-share tables by using the "corrected" dose d_c, where

$$d_c = d_o/(1 + \omega\ d_m). \qquad \text{(III-6)}$$

IV

ASSUMPTIONS ON RISK ALLOCATION AND DOSE-RESPONSE RELATIONSHIPS

Estimating the assigned share for radiation as a cause of cancer in an exposed person requires assumptions about:

- Baseline cancer incidence rates stratified according to age, sex, and other risk factors deemed important in estimating assigned shares.

- Dose-response relationships for cancer risk consistent with epidemiologic data, laboratory experiments, and radiobiologic and mathematical theory.

- Variation of dose-response relationships with dose rate and radiation quality (low-LET versus high-LET radiation).

- Methods for handling the latent period between exposure and diagnosis. Can it be estimated as an integral part of the risk analysis or must it be assumed a priori?

- Duration of the period over which the excess carcinogenic risk is expressed and risk-projection methods for smoothing within and extending beyond the period of observation.

- Adjustments for competing and possibly interacting risk factors, such as occur with smoking and lung cancer.

Two types of assumptions about models for extrapolating or projecting risks to situations on which observations are lacking or insufficient are especially important. The first deals with the estimation of excess risk in categories of the population, and the

second, with the estimation of risk at doses far below those observed in the data.

A. Risk Allocation

For a given exposure to radiation, epidemiologic studies provide information on the total excess cancers observed in specific groups of people. To create tables of assigned shares, it is necessary to estimate how the excess risk varies with time after exposure and among differing populations at risk. This section discusses several important issues concerning these estimates.

1. Relative-Risk versus Absolute-Risk Models

An epidemiologic study in a human population exposed to radiation observes the number of cancers that appear in a period (or several periods) in comparison with those appearing in another, similar population not exposed to the radiation. Because the observed population is generally small, even when the comparison population is not (as when the average national experience is used for comparison), the numbers of cancers in short age intervals or for persons exposed at specific ages can be vanishingly small. Thus aggregation or smoothing of data collected over several short periods has been resorted to, with the idea of getting a more reliable estimate of the age-specific risk associated with exposure. Another motive for grouping the published data is to reduce the number of pages necessary to convey the information. For example, the data on the atomic-bomb survivors in Hiroshima and Nagasaki are often clustered in intervals of 10 or 15 years for age at exposure and intervals of 4 years or more for age at detection of cancer. The Japanese data tell how many cancers in excess of those expected have occurred in each interval since 1950. To create tables of assigned shares, we want to estimate age-specific excess-cancer rates for any time since exposure, using as many as possible of the data on the Japanese collected over the 30-plus years since 1950

and whatever we can reconstruct of the data on cancers arising in them between 1945 and 1950.

Allocating risks over time requires a mathematical model of the cancer induction pattern. The simplest type of model may be a statistical smoothing technique that assumes only that the risk ought to vary smoothly from one age to the next. The patterns observed could differ from one type of cancer to another, from one age at exposure to another, and from one cohort of exposed persons to another. Consistency in every model is not necessary. However, scientists prefer methods that enable them to develop and test hypotheses that explain the phenomenon and to predict results for conditions that have not been observed. Therefore, synthesizing assumptions about applicable models are usually invoked. In the radiation-risk literature, the two most common models relating exposed and nonexposed persons are the constant-absolute-risk model and the constant-relative-risk model.

The constant-absolute-risk model assumes that the incidence rate of excess cancers after a given dose of radiation at a given age will (after a latent period) be independent of age. (The treatment of the latent period is examined further in the next section.) More specifically, if h(t:0) is the baseline incidence rate at age t and h(t:d) is the corresponding incidence rate (at age t) for persons exposed to dose d, the constant-absolute-risk model assumes that h(t:d) - h(t:0) is the same for every age. For example, if the excess incidence rate averages 2 per 100,000 people aged 30, then 2 per 100,000 is assumed at every other age after the minimal latent period has elapsed.

In contrast, the constant-relative-risk model assumes that, after the same minimal latent period, the ratio, h(t:d)/h(t:0) of the incidence rate in the exposed group to the baseline rate remains constant with age. Thus, if the incidence rate in a nonexposed population doubles between two ages beyond the minimal latent period, the rate in the exposed group will also double. Note that, because the

baseline incidence rates for most cancers increase with age, the absolute excess risk in a constant-relative-risk model will also increase with age, whereas it remains fixed in the constant-absolute-risk model.

For all cancers except leukemia and bone cancer, the Ad Hoc Working Group has adopted the relative-risk model, pointing to patterns of breast-cancer incidence, especially in Japanese women, and to selected other cancers, such as lung cancer. It concludes that the nature of excess incidence of leukemia is different, with a much shorter minimal latent period and a rapid increase and later slower decrease in excess incidence after irradiation--a pattern that is consistent with neither the absolute-risk nor the relative-risk model. It also uses a similar model for bone cancer, as was done in BEIR III.[50]

The Oversight Committee agrees that the selected wavelike models for excess risk of leukemia and bone cancer are reasonable representations of the general form of the observed data, but is cautious about the manipulations that resulted in the "artificial data set" (p. 89 in the Working Group's draft report) for leukemias occurring earlier than 5 years after exposure. The resulting risk estimates are surprisingly high for some combinations of age at exposure and age at diagnosis, whereas they are somewhat lower for other combinations than other analyses have suggested. These differences probably occur because the risk estimates are quite sensitive, for some times after exposure, to the mean and variance of the log-normal distribution assumed by the Working Group.

The Working Group has adopted the constant-relative-risk model for all other cancers (after a growth from zero risk at 5 years to a constant relative risk beyond 10 years). The Oversight Committee sees good support for this assumption in some data sets (e.g., on lung cancer and breast cancer), but for others, such as stomach cancers, the available data[73] might be more consistent with a constant-absolute-risk model. Similar reservations apply to data on thyroid cancer.

The Working Group seems to imply that these constant-relative-risk models can be used to project beyond 35 years after initial radiation exposure. However, its draft final report is not entirely clear on this point: some data seem to cut off after 30 or 35 years, and others continue much longer. When data become available to permit their determination, it is conceivable that relative-risk estimates for times long after first exposure could fall or (much less likely) rise. A decrease could occur for solid tumors if, as seems possible for leukemia, the effect of radiation was to bring the diagnosis of cancer forward in time by adding new initiating events early in life, with the other initiating events and promotional events occurring when they would have occurred in the absence of radiation. Alternatively, particular individuals in the population could be especially susceptible to the effects of radiation, so that the cancers induced by radiation might occur early, with decreasing risk later as the susceptible persons were removed from the population. Thus, relative risks might fall and the absolute risk of radiation exposure might be much less for the period more than 35 years after first exposure.

The available data do not resolve this issue, but there are indications that the answer might vary according to the type of carcinogenic exposure. For example, some data suggest that the cumulative lifetime excess risk of lung cancer from alpha radiation in nonsmoking miners could be very similar to that for smoking miners.[55] However, there is an early increase in risk in smoking miners and only a later increase in nonsmoking miners.

The Oversight Committee recommends that the Working Group provide explicit guidance on projecting risks beyond the period of observed data or at least an explicit statement that it cannot do so. (Recommendation 7).

The variety of patterns of excess incidence over time makes the choice of a model somewhat arbitrary for cancers on which data are

sparse. Perhaps the most attractive argument for choosing one model over the others is simplicity; i.e., the constant-relative-risk model produces constant assigned shares over time, thus reducing the volume and complexity of tables needed. However, note the caution in Section II H regarding convenient assumptions.

Because of the uncertainty associated with the selection of a time projection model, we recommend that the Working Group explain in greater detail the consequences of the various models being considered, so that the users of the tables may understand the limitations of the models. (Recommendation 6)

For example, if the baseline risk increases with age for a given type of cancer, the use of a constant-relative-risk model when a constant-absolute-risk model is appropriate will tend to lead to underestimates of assigned shares of causation for persons whose cancers are diagnosed relatively soon after the minimal latent period and overestimates for persons whose cancers are diagnosed long after exposure. The size of bias in estimates depends on the extent to which the assumption about constant relative risk is violated; this effect could be illustrated with examples. Several numerical examples of this phenomenon would contribute to the understanding of one aspect of uncertainty.

Because no time-projection model is likely to describe the response to radiation for all types of cancer other than leukemia and bone cancer, the Oversight Committee recommends that the assumption of constant relative risks be reassessed as new data and new methods of analysis appear. (Recommendation 10)

2. Interval between Exposure and Detection of Tumor

The interval between exposure to radiation and detection of a tumor that may have been caused by the radiation varies from one tumor to another and may be many years, often decades. The process that takes

place between the initial exposure to radiation and the diagnosis is complex and not completely understood. Presumably, if radiation produces an initial precancerous lesion, it is converted into a tumor by some event or process, which may or may not be due to radiation and whose occurrence is distributed in time after the initial event. The proliferation of cancer cells is a complex process that depends on the kind of tumor, its organ or tissue site, and its environment. For example, a breast tumor may lie dormant until shortly before the affected person reaches the age when breast tumors tend to occur naturally, at which time--perhaps after the occurrence of hormonal changes in the breast--an acceleration in growth takes place that leads to a tumor large enough to be noticed. This interval between exposure and diagnosis is the latent period. Clearly, the diagnosis of the tumor also is distributed in time and cannot occur immediately after the initial event. The latent period therefore may be very short, although this is unlikely, or it can be long if the conversion events are delayed or if the environment of the cancer is not conducive to its growth.

It is clear that both age at exposure and relevant cancer site are likely to influence the distribution of cancers over time after irradiation. Recognizing that no cancer could develop immediately after exposure to radiation, radiobiologists and epidemiologists have spoken in terms of a minimal latent period before the radiation can be considered to be a plausible cause of cancer in a specific person. This minimal latent period is likely to depend on age at exposure (because age-dependent factors other than radiation are probably involved) and on the type of cancer; but little information on that dependence has been generated, except that leukemias and bone cancers seem to have a shorter induction period than most other types of cancer. On the basis of BEIR III and other authorities, the Working Group in its December 1983 draft report chose 2 years as the minimal latent period for leukemias and bone cancers and 10 years for all other cancers. In our interim report, we noted that, for leukemias and bone cancers, the estimates of risks rose smoothly from zero after the

minimal latent period, but jumped abruptly for the other cancers. We recommended a smoothing function to avoid that discontinuity, and the Working Group adopted a cubic function from 5 to 10 years that, when expressed as annual steps, results in an almost maximal assigned share from 8 to 9.9 years after exposure and a minimal assigned share from 5 to 6.9 years; from 7 to 7.9 years, half the assigned share at 10 years and beyond would be applied.

This solution is better, but could be improved further. First, the method is independent of age at exposure and type of cancer. It is clear from the experience in Japan and elsewhere that the effect of radiation is not detectable--and may not even be possible--until a person has reached the age at which baseline cancer risks first begin to rise.[40] Thus, for a person first exposed at age 15, it might be more appropriate to adopt a 15-year latent period for breast cancer. Other cancers might prove to have minimal latent periods shorter than 5 years for some ages at exposure.

Second, the cubic smoothing function is arbitrary and needs to be reconsidered when better analyses of the human data become available. Whether it should apply over 5 to 10 years or over some other period also needs to be reexamined. The Oversight Committee recommends that consideration be given to allowing different minimal latent periods and different lengths for the period during which relative risks increase for each type of cancer and each age at exposure. (Recommendation 9)

Third, the stepwise increase in the risk is still discontinuous and forces assigned shares to be substantially different between latent periods of, say, 6.99 years and 7.01 years. Although the approximation is necessary if shares are to be tabulated in annual increments, it is not if an algorithm is the principal tool for assigning shares.

Last, as explained in Section III D, prior selection of a minimal latent period and a smoothing function is unnecessary if the time dependence can be subsumed in the overall model. (Recommendation 8)

3. Projection from One Population to Another: Additive- versus Multiplicative-Risk Models

The above discussion has focused exclusively on the estimation of excess incidence in a single category of persons after exposure. Two related questions arise: How can information from one category of a population (e.g., nonsmokers) be applied to another category of the population (e.g., smokers)? How can excess risks observed in Japan be projected to the United States population (or those observed in any population projected to another population whose baseline cancer rates--for nonirradiated persons--are different)?

The two most commonly used models to address the first question are the additive and multiplicative models. An additive model, when used in conjunction with a constant-absolute-risk model, assumes that the excess incidence from radiation in one category is the same as the excess in another category, even though the baseline incidence rates in the categories may differ (see Figure IV-1). In contrast, a multiplicative model (in the context of a constant-relative-risk model) assumes that the relative risk (the ratio of rates in the exposed and nonexposed groups) is the same in all categories of the population. Thus, if the relative risk associated with radiation in nonsmokers is 2, the risk in exposed smokers will be twice that in nonexposed smokers, regardless of the baseline incidence rates of nonsmokers and smokers. Data on the risks of lung cancer from asbestos seem to follow the multiplicative model better when projected from nonsmokers to smokers.[48]

If the interaction between cancer risk factors proved to be multiplicative and if the time pattern of risk followed the constant-relative-risk assumption, the assigned shares would be the same in all cohorts and for all ages at diagnosis. Some authors (such as Whittemore and McMillan[74]) believe that the data on lung cancer in uranium miners support a multiplicative model for radiation exposure

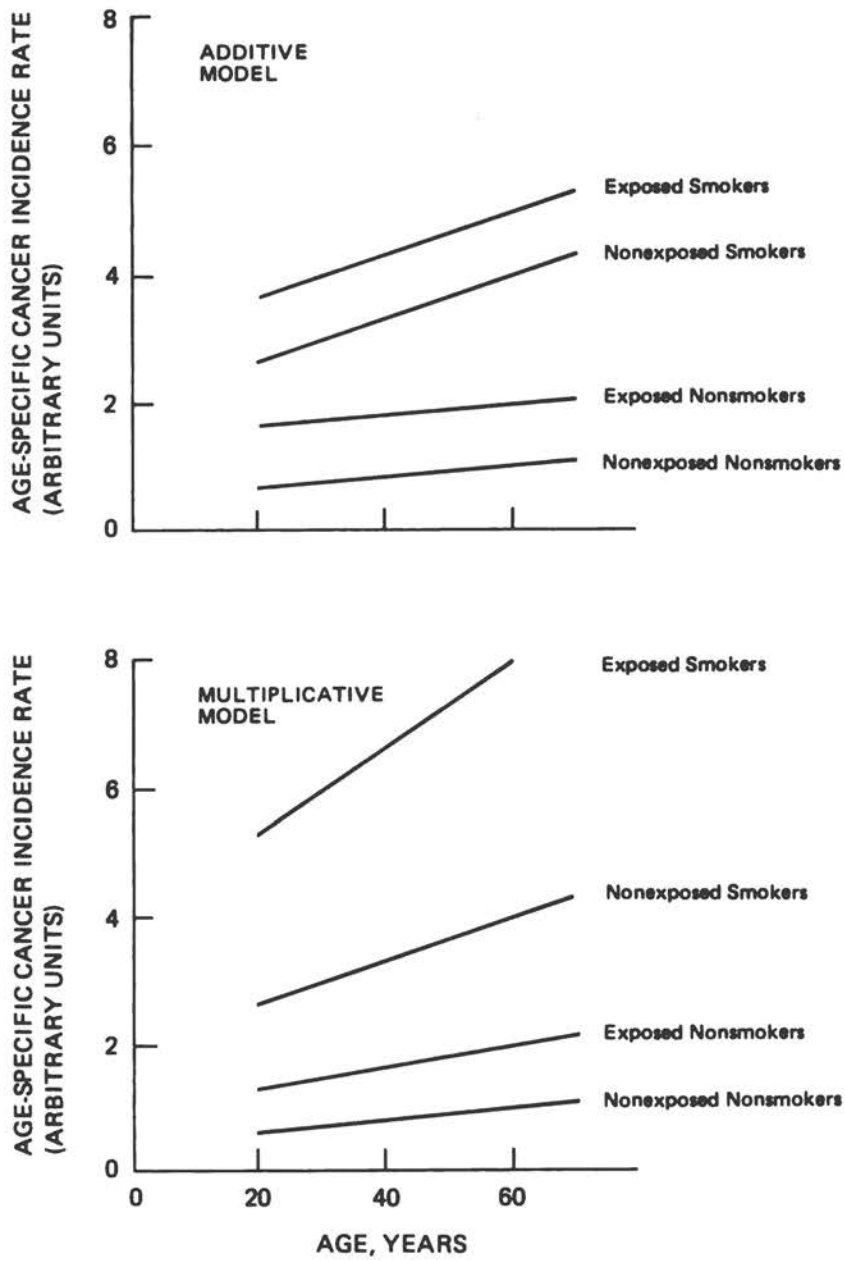

FIGURE IV-1 Additive and multiplicative models for projecting from one population (e.g., nonsmokers) to another (e.g., smokers). Top, additive model assumes that excess risk due to radiation is independent of age, after minimal latent period has elapsed, and is same in both populations. Bottom, multiplicative model assumes that relative risk (ratio of rates in exposed to rates in nonexposed) is independent of age, after minimal latent period has elapsed, and is same in both populations.

in smokers and nonsmokers. The report of the Ad Hoc Working Group uses a multiplicative constant-relative-risk model for all cancer types other than leukemia and bone cancer and for all risk factors other than smoking. Smoking is assumed to act additively with low-LET radiation, but multiplicatively with high-LET radiation.

A second type of assumption is related to the transfer of radiation-risk estimates derived from other populations, specifically the Japanese population, to the general population of the United States. When the risk coefficients were developed by the BEIR III committee, the absolute excess risk over a period of observation was assumed to be the same in any geographic location and independent of the baseline risks in the populations there. The Working Group has accepted the BEIR III coefficients (or equivalent) as valid in the United States in the aggregate, but has assumed a special time dependence, differing according to the site of the cancer. It assumes a special wavelike model for leukemia and bone cancer and a constant-relative-risk model for all other cancers. To derive the coefficients for these time-projection models, the Working Group adjusts the average absolute-risk coefficients, which were derived mainly from BEIR III and based mainly but not completely on the Japanese data, by using a U.S. life table and the U.S. baseline rates from the SEER data base. This adjustment is equivalent to assuming that the same aggregate excess risk would be seen in the United States as in Japan for a period of observation (labeled "Years Follow-up" on p. 97 of the Working Group's draft report). See Appendix F for a more detailed explanation of this adjustment. The Oversight Committee points out that there is also justification for a direct application of the Japanese relative-risk coefficients to the U.S. population. Furthermore, as explained in Appendix B, there is a mathematical inconsistency in the Working Group's approach that puts its validity in question, except when the baseline Japanese and U.S. incidence rates are proportional for the cancer site considered.

Therefore, we recommend that, in the next revision of the tables, this assumption by the Working Group be carefully reexamined in the light of the potential inconsistency that arises when Japanese and U.S. baseline rates are nonproportional. (Recommendation 11)

B. Dose-Response Relationships

The shapes of the dose-response curves for radiation and their dependence on dose rate have been debated for many years, and the current efforts to create tables of assigned shares will not conclude the argument. Partly as a result of suggestions in our interim report, the Working Group has adopted a linear-quadratic dose-response model for most cancers, the exceptions being thyroid and breast cancers, for which the dose-response relationship is assumed to be linear. The linear-quadratic assumption stems principally from selected observations in laboratory animals or cell cultures and from radiobiologic theory.

For most, if not all, cancers, not enough human data exist to distinguish between linear and linear-quadratic hypotheses or even to reject other possible relationships. The Working Group chose the linear relationship for thyroid and breast cancers on the basis of epidemiologic studies that seem most consistent with it, but even for them the conclusion can be challenged. However, the reasoning that leads from theoretical and laboratory results to the use of a linear-quadratic hypothesis is also subject to challenge.

Some scientists would prefer greater use of the linear hypothesis on the grounds that it is simple and has not been convincingly disproved. Others believe that the combined evidence from epidemiologic, laboratory, and theoretical studies on balance favors a curvilinear relationship, arguably linear-quadratic, even for thyroid and breast cancer. The linear-quadratic hypothesis would produce lower risk estimates than the linear hypothesis at low doses.

The Oversight Committee notes that the Working Group may have had little choice in the dose-response models that it could consider once it chose to use BEIR III risk coefficients as its starting point. A new analysis of both the data available at the time of BEIR III and data made available since then might incorporate the dose dependence with other dependences, such as those on age at exposure and age at diagnosis.

On balance, the Oversight Committee welcomes the flexibility of the Working Group in allowing for more than one dose-response relationship, with the choice for a particular cancer type dependent on available data. The following discussion therefore lays out some of the arguments for various dose-response hypotheses and related assumptions about the effect of dose rate or radiation quality for consideration when the tables are revised.

1. Fundamentals

In epidemiologic studies of radiation-induced cancer, the statistical uncertainties associated with observations of excess cancer at low doses prevent the unambiguous assignment of radiation risks at these doses. In the absence of compelling data, it is necessary to choose a dose-response relationship that will permit risk estimates to be made at the lower doses, particularly in the range of 1 to 100 rads (0.01 to 1 Gy), in which estimates of assigned share will be called for most often. The magnitude of the risk might depend more on the relationship adopted than on the actual data, if any, at those doses. Human data that positively argue for one dose-response model over another are absent for a wide range of cancer sites.

2. Extrapolation from High to Low Doses for Low-LET Radiation

In recent years, a general hypothesis for estimating excess cancer risk in irradiated human populations has suggested various and complex dose-response relationships between radiation dose and observed cancer

incidence.[47,50] Among the models for cancer induction by radiation is one based on theoretical considerations, on extensive laboratory animal studies, and on limited epidemiologic surveys. This multicomponent dose-response relationship initially curves upward and contains both linear and quadratic functions of dose (which represent the process of cancer induction by radiation). At higher doses, it is influenced by a modifying exponential function of dose (which represents the competing effect of cell inactivation at high doses).[47,50,69] It is likely that the dose-effect relationship will differ for different tumor types or for radiation of different LET.[24]

At low dose rates, three relationships of response to dose of low-LET radiation have received the most support and are credibly related to mechanisms of radiation carcinogenesis: the linear, the linear-quadratic, and the quadratic.* Some support for each of these relationships can be found in epidemiologic studies of various types of cancer under various conditions of exposure. Although the balance of evidence from laboratory research tends to support the linear-quadratic relationship, support for the others can also be found.

In particular, a recent review of Nagasaki Tumor Registry results for the Japanese atomic-bomb survivors[74] found that

> the Q model fits better in the statistical sense (smallest X^2 value and largest tail probability) than the L or L-Q models for leukemia, and the quadratic term in the L-Q model is positive although not statistically significant. The Q model does not fit the incidence data on all cancers except leukemia, where the L and L-Q models fit equally well. The linear term is significant in the L-Q model, whereas the quadratic term is not. Thus the linear model appears to be the better for all cancers except leukemia. A similar tendency was observed for several specific sites of cancer, i.e., cancers of the lung, breast, thyroid, and stomach; the Q model either does not fit (for breast cancer) or fits more poorly than the L or L-Q model, and the quadratic term in the L-Q model does not differ from zero (the calculated value is negative). These findings, when compared with the analysis of the fit of these models to cancer mortality in 1950-1978, where the neutron component was also considered, are seen to be very similar.

*L = linear; L-Q = linear-quadratic; Q = quadratic.

Figure IV-2 shows both the observed data for six cancer sites and fits with each of the three models. Although Wakabayashi et al. were not entirely clear on this point, the measure of radiation appears to be air kerma in rads, not absorbed dose to specific organs. The analyses are not specific for age at exposure or age at diagnosis; a desirable future activity is to conduct sex- and age-specific analyses for each organ site. The shape of the response curve appears to be different for different tumor types; thus the assumption of identical shape for all tumors except thyroid and breast, as assumed by the Working Group, is unlikely to prevail as better data become available.

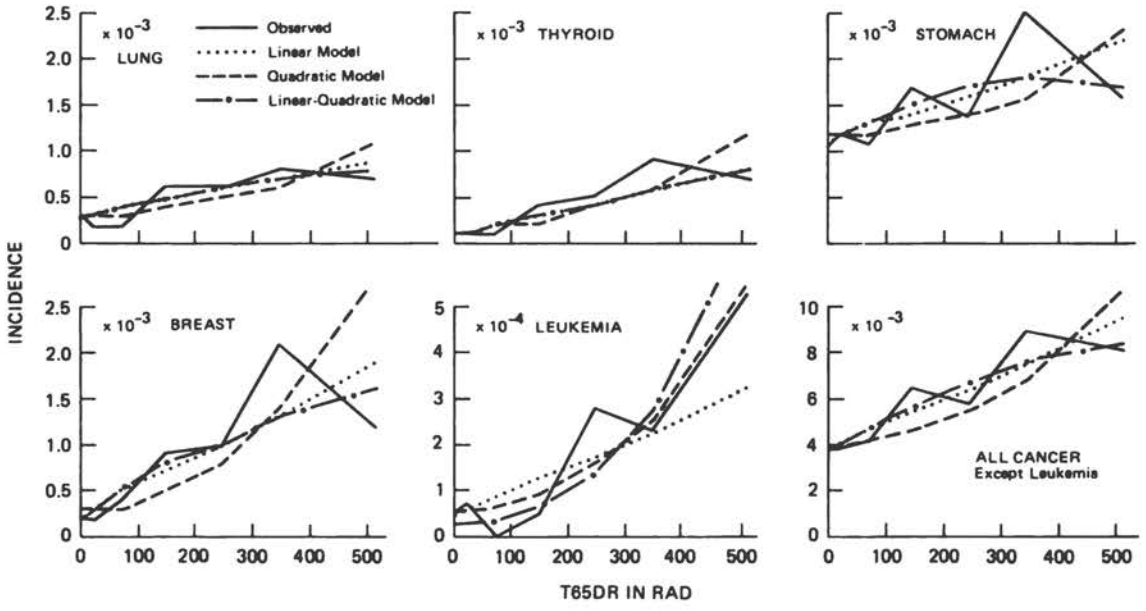

FIGURE IV-2 Observed and expected average annual incidence of selected cancer sites, 1959-1978. Reprinted with permission from Wakabayashi et al.[73]

Inspection of the plots in Figure IV-2 suggests that poorly understood factors--possibly including cell-killing--may have influenced the data from the groups at the highest kerma, because the observed incidence decreases at high kerma for five of the six sites. The plots also give the impression of a decrease in incidence at less than about 100 rads (1 Gy). If one examines the grouped data (adjusted for sex and age), but omits the point at the highest kerma, a quadratic model may provide a better fit for some organs (e.g., lung and thyroid). Although this reexamination is exploratory, it indicates that both linear and curvilinear models deserve attention and that models more complex than the linear-quadratic might be investigated.

The recent study by Brodsky *et al.*[11] described in Section III D provided an analysis of leukemia mortality that was age-specific and time-specific, with some grouping. Brodsky *et al.* found that several of the coefficients in the dose-response model were time-dependent. Age at exposure also plays a role later after exposure. All models tested are constrained to produce positive probabilities and to be linear in neutron kerma, but may have both linear and quadratic terms in (low-LET) gamma kerma. The authors found that a model that is linear in both types of radiation and another that is linear in neutron kerma but quadratic in gamma kerma both fit the data when and only when age at exposure and time after exposure are included. According to the authors, the model that is quadratic in gamma kerma fits the data slightly better ($p > 0.25$) than the one linear in gamma kerma ($0.1 < p < 0.25$). The linear-quadratic model does not fit these data. The data can be examined in a different way; with the alternative approach, the linear model fits slightly better than either of the other two models. In neither analysis are the differences significant.

These two recent studies of the Japanese atomic-bomb survivors demonstrate that the debate over the shapes of dose-response relationships is far from over. Both the linear assumption and the

linear-quadratic assumption--particularly with a universal crossover dose of 116 rads (1.16 Gy)--will be challenged. Appendix G discusses how various hypotheses about mechanisms would influence the dose-response relationship and presents laboratory evidence that bears on these hypotheses. Section IV B of our interim report (Nattional Research Council, 1984b) discusses the evidence, especially for the linear-quadratic model, in more detail. Because the nature of the dose-response relationship may depend on conditions other than dose, the Oversight Committee recommends that new data analyses should take into account sex, age at exposure, and age at diagnosis whenever possible. (Recommendation 12)

3. High-LET Radiation and Internal Sources

Sources of exposure to high-LET radiation may be either external or internal. The detonation of a nuclear weapon is an external source of high-LET neutrons; inhaled radon gas and especially its less-volatile internally deposited decay products are internal sources of high-LET alpha particles.

It is known that a few of the service personnel exposed at the nuclear weapons tests received neutron doses[26] and that uranium miners have been exposed to alpha particles from the decay products of inhaled radon.

Experimental evidence shows clearly that the carcinogenic effect of high-LET radiation is greater per unit dose than that of low-LET radiation. The increase in effect is associated with the densely ionizing track of these heavy particles. It has long been thought that the human experience in Hiroshima and Nagasaki confirmed the experimental evidence of the increased effect of neutrons, but the revision of the dosimetry now makes that uncertain. The dosimetry of high-LET radiation is complicated, for example, because the energy deposition from alpha particles in the lung is notably different from

that from low-LET radiation in the cell and is localized in particular parts of the lung.

The information available on the dose-response relationship for high-LET radiation is generally considered to be most consistent with a linear model. However, the curves often show saturation for only moderate doses of high-LET radiation. The precise explanation for the bending over is unknown; and, because the curves bend over at relatively low doses, linear interpolation of data obtained at high doses may underestimate the response at low doses. The review of lung-cancer risks from radon recently published by the National Council on Radiation Protection and Measurements,[46] the model proposed by Harley and Pasternack,[28] and the previously cited paper by Whittemore and McMillan[74] provide a basis for estimating risks from high-LET alpha radiation.

The Working Group does not specify how doses from internal emitters are to be calculated, but leaves this effort to the users of the tables. Once an appropriate organ dose has been calculated, the Working Group suggests that it be multiplied by a quality factor to derive a dose equivalent (in rems or sieverts) with which to enter the tables. Uniform quality factors of 20 for alpha radiation and 10 for neutron radiation are proposed. The Working Group appears to have assumed that these quality factors come from a comparison of the dose-response relationships for high-LET radiation with the linear dose-response relationship for low-LET radiation. Thus, when the Working Group uses a linear-quadratic model for a particular cancer, it applies an additional factor of 2.5 to the linear coefficient (the slope of the curve at low doses).

The Oversight Committee is uncertain that the additional adjustment of 2.5 is justified or consistent with the practices of such radiation standard-setting bodies as the International Commission on Radiological Protection (ICRP). ICRP Publication 26 specifically states[32] that quality factors "are intended for use in radiological protection" and

that "radiation risk estimates should be used with great caution," in recognition of the possibility that the actual risk of low-LET radiation at low doses may be lower than that predicted by a linear extrapolation. In determining dose equivalents for alpha particles and fast neutrons, the ICRP appears to have applied quality factors to a linear dose-response model from which the risks of low-LET radiation have been estimated for low doses and low dose rates. Thus, it may not be correct to apply the reported quality factors for neutrons or alpha particles to the linear dose-response model to derive excess cancer risks for high-LET radiation. The Oversight Committee recommends that the Working Group reassess its proposed adjustment to make sure that it is justified by available information. (Recommendation 13)

The quality-factor concept was developed with a linear dose-response model in mind and is not easily applicable to a curvilinear dose-response relationship. Relative biologic effectiveness (RBE) values may be more relevant to the epidemiologic circumstances of alpha-particle exposure. Or it may be possible to develop tables that operate directly on exposures measured in working-level months, derived from epidemiologic evidence on miners, as was proposed by Whittemore and McMillan.[74] A method for estimating assigned shares for persons exposed to high-LET radiation, especially from internal emitters, should be developed that does not depend so heavily on the estimates for the effects of low-LET radiation. (Recommendation 14)

4. Protracted and Fractionated Exposures

Quantitative estimates of the risk of cancer from exposure to radiation depend heavily on data from studies of the Japanese survivors in Hiroshima and Nagasaki, in which the total dose was delivered in a single exposure of short duration and high dose rate.[73] In other populations studied, the radiation exposure was often spread out over time at lower dose rates or was delivered at intervals, with each subdose at a high dose rate.[7] When radiation is received at relatively high dose rates but in relatively small doses separated in

time by a day or more, it is said to be fractionated, as in medical fluoroscopy of women treated for tuberculosis.[8] Radiation can also be delivered continuously or almost continuously over a relatively long period at low dose rates, as in the inhalation of radon and its decay products by workers in uranium mines.[46] If the protraction of radiation at low dose rates extends over a substantial portion of a lifetime, the risks of cancer induction may be influenced not only by the reduction in dose rate, but also by changes in susceptibility to cancer induction with age.

For a given total dose of radiation, lowering the dose rate or fractionating the exposure may change the risk of developing cancer at a given time after first exposure. The direction and magnitude of the change may depend on the quality of the radiation (high- or low-LET) as well as on whether it is protracted at relatively low dose rates or fractionated at relatively high dose rates.

The laboratory evidence concerning the effects of lowering the dose rate of low-LET radiation is suggestive, but far from convincing, for estimating cancer risks in human populations. Some scientists discount the relevance of animal and cell experiments for assessing the influence of dose rate on cancer incidence in humans. The following discussion of observations of dose-rate effects at high total doses is offered for whatever insights it may provide. Studies on cultured mammalian cells and on laboratory animals indicate that reductions in dose rate for low-LET radiation, such as x rays and gamma rays, generally decrease the observed radiation effect per unit dose. In experiments on chromosomal damage, effects are often reduced by about a factor of 3 for high total gamma ray doses.[54] A pronounced dependence of germ cell mutations on dose rate has been observed in a wide variety of organisms, particularly mice. In irradiation of male mice, mutations are lower at low dose rates than at high dose rates by a factor of about 3; this factor was adopted for protection guidance regarding genetic effects.[32] Reduction of effects with increasing protraction of dose has also been observed in experiments on the

malignant transformation of cells,[27] on lifespan shortening in rodents,[65] and on cancer induction in animal populations.[67,68]

Fractionation of low-LET radiation, compared with single acute doses, has been observed to reduce excess cancer incidence in animal populations and also to increase it. In mice, for example, risk was reduced for skin tumors[13] and acute myeloid leukemia.[43] Other data indicate that fractionation does not always reduce the effect of low-LET radiation; the conditions of exposure (total dose, dose per fraction, number of fractions, and interval between fractions) appear to be important. For example, splitting x-ray doses greater than 150 rads (1.5 Gy) into two fractions reduced the transforming effect on fibroblasts in vitro,[42,64] but splitting smaller total doses increased the rate of malignant transformations.[42] Dividing the dose into five daily fractions decreased the effect of cobalt-60 gamma radiation.[20] In mice susceptible to the induction of thymic lymphoma, dividing large doses into fractions of about 150 rads (1.5 Gy) was more effective than delivering a single dose.[35] Interaction of the temporal dose distribution with cycles of cell repair and cell susceptibility to inactivation has been suggested as the basis for responses of this type, but the basic mechanisms and kinetics of such effects are uncertain.[50]

The BEIR III Committee[50] recognized from the experimental evidence that both dose rate and fractionation may affect the risk of cancer induction, but believed that the information available on man was insufficient to adjust for it. In the case of radiation-induced breast cancer, the fact that multiple low-dose exposures did not appear to produce fewer cancers per unit dose than a single exposure[8] suggested to the Committee that in this case radiation damage is cumulative and that highly fractionated x radiation may be approximately as effective as nonfractionated radiation in inducing breast cancer.[50] The results of the study of breast cancer in radium-dial painters by Baverstock et al.[5] are consistent with the hypothesis that dose rate is not important. The studies by Boice and

Monson and by Baverstock et al. have been criticized for being unable to detect such an effect if one had been present. The situation for thyroid cancer induction is also complicated. In children treated with x rays, Shore et al.[62] saw no fractionation effect, but followup of persons receiving radiation from administered iodine-131 suggested considerable reduction in excess incidence of thyroid cancer, compared with that in persons externally irradiated with x rays at high dose rates.[31] Ron and Modan[58] found the evidence of a fractionation effect to be equivocal in the data on thyroid cancer following irradiation for tinea capitis.

When protraction or fractionation reduces the effect of radiation, it is likely that some of the damage caused by low-LET radiation has been repaired because the absorbed radiation energy was sufficiently spread in space and time.[47] One hypothesis is that lowering the dose rate reduces the probability of interaction among tracks of low-LET radiation and is similar in effect to lowering the total dose; see Appendix G.

The decrease in effect for low dose rates or fractionation does not appear to obtain for high-LET radiation, such as neutrons and alpha particles; on the contrary, there appear to be mechanisms that sometimes increase the observed effect per unit dose for exposure to high-LET radiation when the dose rate is reduced in man or animals. For example, the risk of osteosarcoma from the intravenous therapeutic administration of preparations containing radium-224 appears to be higher for a given total radiation dose if the dose is administered over a period of a year, rather than over a period of months.[41] Experimental data also indicate that a reduction in dose rate of high-LET radiation may increase the induction of some cancers in animals[44,67,71] and malignant transformation of cells in vitro.[30] Similarly, some fractionation patterns increase the effect of life-shortening,[3,63] cancer induction,[3,67,71] and malignant transformation in vitro.[27] In the case of low total doses and small

doses per fraction, fractionation may not make any difference in effectiveness per unit total dose.[24]

The Working Group has addressed the potential effects of fractionation of dose or decreased dose rate for low-LET radiation on the basis of the linear-quadratic dose-response relationship. Using consistent reasoning, it makes no adjustment for dose-rate effects in risk estimates for thyroid and breast cancer, where it uses a linear model. If these cancers later prove to follow a curvilinear dose-response relationship, a dose-rate adjustment may become necessary. Similarly, the Working Group makes no allowance for dose-rate effects in risk estimates for high-LET radiation, where it also uses a linear model.

The method used by the Working Group to account for a possible reduction in risk appears to have arbitrary elements, such as the 24-hour division between acute and chronic exposures. It also seems cumbersome to apply. Accordingly, although the Oversight Committee does not disagree with the method, it recommends that it be presented more clearly and that the Working Group state its underlying scientific assumptions about the potential interactions of exposures separated in time. The approach may be clarified by graphic displays. (Recommendation 16)

The Working Group has, in its method, apparently treated the effects of low dose rates and fractionation as manifestations of partial or complete repair of radiation injury, with the degree of repair dependent on the time pattern of dose delivery, total dose, and radiation quality. Depending on a number of factors, the method can lead to an overestimate or underestimate of the radiation risk and, hence, of the assigned share. This may have little practical impact, inasmuch as most exposure conditions will constrain the risk estimates to the low-dose portion of the dose-response curve, where the response is nearly linear and dose-rate effects are less likely to be important. Nevertheless, the method can lead to confusion, permitting different

interpretations by different users of the radioepidemiologic tables. A method less subject to a variety of interpretations would be preferable.

Although data to do so are probably not available, in the long run it may prove desirable to include the potential effects of dose rate and fractionation directly in a comprehensive dose-response model that also takes into account age at exposure and age at diagnosis, with a smooth variation in response to changes in dose rate or any other variable. The Oversight Committee recommends investigation of the possibility of creating such a model as data accumulate. (Recommendation 17)

V

SELECTION OF DATA

Once appropriate epidemiologic, statistical, and radiobiologic assumptions and methods have been chosen, other choices need to be made regarding the data sources to be used and the cancer sites for which assigned shares will be estimated. This chapter discusses the principal sources of data on baseline and radiation-related risks and on the sites where radiation-induced cancers appear to be found.

A. Cancer Incidence and Mortality Data

Cancer mortality data, derived as they are from death certificates, are available for the entire United States and are codified in an internationally standardized manner for underlying cause of death. Incidence data are obtained from registries that attempt to register all cases of cancer occurring in a defined population. Their completeness and accuracy depend on careful prospective surveillance of a population defined by demographic characteristics and residence and require continuing evaluation of various sources of case reporting and review of vital records.

The choice of a reliable compilation of cancer incidence data applicable to the U.S. population as a whole may be limited to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.[76] If any projection model other than a constant-relative-risk model is used to predict the risks in one population from the experience in another, reliable incidence data are required for estimation of assigned shares. The SEER data appear, in general, to fulfill this requirement best, but nevertheless have limitations.

The SEER program, which followed the Third National Cancer Incidence Survey of 1969-1971, has been in effect since 1973. The SEER data do not represent a random sample of the United States, but instead report the cancer incidence and mortality data from 11 regions (including Puerto Rico) that maintain population-based cancer reporting systems that are considered to be reliable. Those cancer registries have been selected to provide data on cancer risks for various population characteristics--including race, age, and sex--according to tumor sites. The total coverage is approximately 10% of the U.S. population. Although the SEER data base has been described as adequate to characterize the incidence of cancer nationwide, it might prove useful to investigate how national rates would change if different weights were applied to the different registries according to their mixes of population characteristics. The Oversight Committee sees no alternative to the decision of the Ad Hoc Working Group to use the SEER program for baseline cancer rates in estimating the tabulated assigned shares. The Working Group has chosen to use 10 of the 11 regions and has not included the Puerto Rico registry.

The SEER data provide indexes only since 1973, but might be more reliable than data from the preceding three National Cancer Incidence Surveys. The greater efficiency of registration of the SEER program and changes in registration areas may explain in part the apparent increases in cancer incidence in recent years, in the face of stable or decreasing mortality rates for many cancer sites. These changes can introduce perturbations in the computation and use of assigned shares, because corrections need to be made for cases originating a decade or more ago. This should not seriously affect present or future estimates of assigned shares, particularly if the greater efficiency of registration of the SEER program is maintained.

There are no easy solutions to the problems of variations in recorded rates or competing risk factors that distort incidence or mortality rates in the various geographic regions of the United

States. The recorded cancer rates vary from one locality to another, and also within localities, when cancer category, age interval, and sex are held fixed. The effect of race on cancer rates can be sizable and can differ between localities or sexes. The rates shown in the SEER data base include any cancers related to radiation. Thus, they are not truly baseline rates in the sense of representing a population entirely nonexposed to the radiation of interest, and in principle they need to be corrected before being used in assigned-share calculations. It is doubtful, however, that such population-based rates are substantially affected by radiation.

The Working Group has chosen not to consider ethnic and geographic variation in the SEER cancer rates when estimating assigned shares. Although it recognized that these factors varied considerably for some site-specific data, it did not assess how much the assigned shares might change if these variables were included in the partition of the population. In future revisions of the tables, the influence of these decisions should be identified and evaluated, particularly as they affect SEER cancer rates and thereby estimation of assigned shares.

Although the SEER data have other limitations, few alternatives could be considered for estimating assigned shares. For example, other incidence or prevalence data are available--such as National Center for Health Statistics surveys and state and hospital tumor registries--but none provide comparisons of medically verified incidence data with mortality data based on death-certificate ascertainment. No better set of incidence data for the U.S. population appears to be available than the SEER data.

Doll and Peto[19] have noted the shortcomings of both cancer incidence and mortality data and concluded that mortality data are more trustworthy. Mortality data are most often used in assessing cancer incidence trends.[18,19] Analysis of trends can provide information on changes in prevalence of risk factors, but for some cancer sites mortality data are not satisfactory for such analysis. For thyroid

cancer, in which survival rates are high, mortality rates will underestimate incidence rates; changes in survival will alter mortality rates, irrespective of changes in incidence rates; and the accuracy of death-certificate classification can change over time. The interpretation of cancer trends over long periods is complicated by problems of comparability.[18]

In their recent review of the SEER program, Devesa et al.[18] found considerable variation over time in some indicators of completeness and accuracy of reporting, particularly death-certificate and histologic confirmation. Mortality and incidence trends were examined for cancers of the lung, stomach, colon and rectum, prostate, breast, and uterus in five geographic areas in the United States. Incidence trends were consistent with mortality patterns for some sites, but not for others. Devesa et al.[18] and Doll and Peto[19] concluded that both incidence and mortality data were valuable in assessing cancer trends.

The implication of these observations for the radioepidemiologic tables is that, when trends are occurring in baseline cancer incidence, the assessment of etiologic risk factors should consider both incidence and mortality data. The July 1984 draft report of the Working Group does not appear to use the cancer mortality rates available in the SEER program, particularly for assessing variability of incidence rates over time. The Oversight Committee recommends that the use of mortality data be considered for improving the understanding of the baseline incidence data and for identifying the uncertainties in the trends for those data. (Recommendation 5)

B. Radiation Risk Estimates

Compilations of risk estimates for radiation-related cancers include the BEIR III report,[50] the U.N. Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report,[70] and the ICRP report.[32] Additional relevant scientific reports available in the epidemiologic literature since 1980 include those of Boice and

Fraumeni,[6] Kato and Schull,[37] Prentice et al.,[53] Brodsky et al.,[11] and Wakabayashi et al.[72] Each has limitations; none is sufficiently comprehensive or reliable to provide incidence data necessary for confident estimation of assigned shares, except under narrowly defined conditions. Many of the original data from which all the above reports were derived have been retained and, at least in principle, could be made available for reanalysis with improved techniques.

The ICRP report[32] presented radiation risk coefficients for mortality derived from the UNSCEAR report.[70] The coefficients are coarsely stratified by age; the categories are too broad for effective use in computation of assigned shares. The UNSCEAR report[70] provided an array of age- and sex-specific data that could be used for calculating some radiation risk coefficients, but they, too, were presented only for broad age categories. The UNSCEAR estimates were based almost entirely on mortality data and assumed linearity of the dose-response relationship, with corrections for extrapolating from high to low doses, where data were not available. The BEIR III report,[50] like the ICRP and UNSCEAR reports, provided cancer risk estimates for most cancers associated with low-dose, low-LET radiation exposure, with emphasis primarily on cancer mortality and secondarily on cancer incidence. All three reports dealt with cancer risk estimates in connection with cancer deaths from whole-body exposure to low-LET radiation.

The BEIR III report[50] does provide a basis for determining a limited number of risk coefficients for cancer incidence. The BEIR III committee considered mortality data more reliable than incidence data in the Japanese atomic-bomb and the British ankylosing-spondylitis surveys, but there are problems in deriving risk estimates for a cohort all exposed at the same time. For example, comparison of exposed population cohorts with suitable controls or life tables may be biased when ascertainment is not complete or where there are serious differences in completeness. In the BEIR III report, the cancer-mortality coefficients derived from the Nagasaki Life Span Study

were increased by a factor of 1.23 to correct for incomplete ascertainment.[50, p. 196]

The BEIR III committee developed risk estimates for cancer incidence, as well as cancer mortality, for individual cancer sites in exposed populations (see Appendix A and Table V-14 of the BEIR III report). Estimates from three different methods were combined, primarily because none was considered satisfactory alone.

o Mortality risk estimates derived from the Japanese Life Span Study data were multiplied by weighted ratios derived from available NCI statistics on average site-specific incidence and mortality.

o The Nagasaki Tumor Registry incidence data were fitted to the constrained dose-response models.

o Site-specific risk estimates (except those for leukemia and bone cancer) derived from an array of epidemiologic studies detailed in Appendix A of the BEIR III report were converted to age- and sex-specific estimates and then summed over cancer sites. The sums were used as though equivalent to the risks for all cancers, even though the sum can be an overestimate (see Table V-14 in the BEIR III report[50]).

For leukemia, the data base was from the Nagasaki Life Span Study, and risk estimates were derived from linear-quadratic dose-response relationships fitted to the data. Bone-cancer risk coefficients for whole-body low-LET radiation exposure were derived from the leukemia model, primarily because some of the epidemiologic characteristics of radiation-induced bone cancer were similar to those of leukemia. The Ad Hoc Working Group has chosen to use primarily results from the third method for estimating cancer-incidence risk coefficients as the basis for estimating assigned shares, but has not recorded the limitations of the method or the unreliability of many of the age-specific risk

coefficients for some of the organ or tissue sites that appear in Table V-14 of the BEIR III report.

Estimation of cancer risk from radiation usually emphasizes four epidemiologic characteristics: the size of the study population, the period of followup or time since exposure, the range of radiation dose, and the dose-response relationship. Corrections are often necessary for such factors as demographic characteristics (e.g., age and sex) to produce more reliable risk estimates. For example, in the BEIR III report (see, for example, Tables V-1 through V-4), risk estimates based on the linear assumption differed from those based on the linear-quadratic assumption by about a factor of 2 or 3 at low doses; similarly, those based on the relative-risk projection model differed from those based on the absolute-risk projection model by about a factor of 2 or 3. Such differences, usually considered tolerable in estimating risks for protection purposes, might change substantially the value of an assigned share for purposes of compensation.

A number of limitations in the BEIR III methods could lead to considerable uncertainty. The problems include selection of the dose-response model, selection of the risk-projection model, adjustments for latency effects, and adjustments for competing causes. The BEIR III committee recognized the importance of these factors.

The greatest amount of incidence and mortality data dealt primarily with the influence of age and sex. Age at exposure is now identified as an important influence in cancer risk; the reasons are poorly understood. The effects of age on leukemia, breast-cancer, and lung-cancer radiation risk are good examples of the variation in calculated values. The situation is similar for the influence of sex, primarily for breast cancer, thyroid cancer, leukemia, lung cancer, and colorectal cancer. Much more information appears to be necessary to apply age-specific and sex-specific data to calculation of risk from radiation at various sites (listed in Table V-14 of the BEIR III report) over a broad range of doses and dose rates, but it is clear

that these two determinants substantially influence the estimation of cancer risk values.

The influence of physical factors, such as quality of radiation and dose rate, is incompletely understood; it is difficult to quantify their influence on risk estimates. By and large, the BEIR III committee did not emphasize two factors, dose rate and high-LET radiation, that can govern the calculation of cancer risk. The Working Group's approach to these two influences is discussed in Chapter IV of this report.

The controversy over the effectiveness of neutrons at low doses has been an issue in the use of the Japanese data. However, any resolution of the Japanese atomic-bomb dosimetry will not alter the importance of radiation quality for estimating the effects of neutrons and alpha particles.

The BEIR III committee recognized that reduction in dose rate may decrease the radiation effect per unit dose, particularly for large doses of low-LET radiation. However, it felt, after analysis of the epidemiologic data, that the evidence was too uncertain to permit assignment of a value to any dose-reduction effectiveness factor to adjust for its magnitude. The breast-cancer data, perhaps the best available on effects of protraction of dose, appeared to fit a linear, dose-rate-independent model best, although large uncertainties accompanied these data.

To project the calculated risk coefficients from one study population to another, risk-projection models are required. The BEIR I and III committees[49,50] chose to apply two age-specific projection models to the complex relationship between ages at time of exposure and at development of cancer and the natural incidence rates of cancer in different populations. This requires assumptions as to the duration of the period in which risk is expressed. To correct for these assumptions, the BEIR III committee chose to make two adjustments: to

omit cancers that have high baseline rates, but are only weakly induced by radiation; and to avoid applying risk estimates derived from early periods in life to later periods in life.

The use of Table V-14 of the BEIR III report as a framework for deriving cancer-incidence risk coefficients for Table Vl-1 of the Working Group's draft final report must be reexamined in the future, because of the inherent limitations in the data bases used to construct it. For example, the incidence risks were derived primarily from mortality risks, adjusted by a series of conversion factors (see Table V-15 of the BEIR III report), because the BEIR III committee felt strongly that no reliable U.S. incidence rates were available at the time of its deliberations. The reduction factors derived for this adjustment were the sex-specific, age-adjusted ratios of the risk coefficients for incidence and mortality from comparable life tables. Thus, the site-specific cancer incidence rates in the SEER program and those derived for estimation of BEIR III linear risk coefficients in Table V-14 are by no means the same. Furthermore, for a number of sites, risk coefficients were, in a sense, "averaged" throughout the age partition to construct Table V-14, even though such data on age-specific response were incomplete, or even lacking, in Appendix A of the BEIR III report. In this regard, some risk coefficients in Table V-14 of BEIR III do not agree with those in its Appendix A, and some were not derived from the relevant, but limited, epidemiologic data.

Table VI-1 of the Working Group's draft report departs from Table V-14 of BEIR III by the addition of salivary-gland tumors for one age at exposure, the elimination of early ages for some sites, division by 2.5 to move from linear to linear-quadratic risk coefficients when appropriate, a change in coefficients for ages 0 to 19 for thyroid cancer, and the introduction of some new coefficients for female breast cancer. The latter two changes are possible because of the newest data available from Japan. However, the age dependence of risk in relation to radiation has been only coarsely modeled by the Working Group.

In summing up, the Oversight Committee concludes that the BEIR III report has sufficient limitations to restrict its use in estimating assigned shares. In this regard, the structure of Table V-14 of the BEIR III report appears to require considerable revision. The Working Group has provided new risk coefficients for several sites; the Oversight Committee believes it advisable to evaluate the latest epidemiologic literature and to apply the most reliable results to the calculation of cancer risk coefficients that are age-, sex-, and dose-specific where possible. (Recommendation 4)

C. Organ and Tissue Sites

The epidemiologic evidence indicates that cancers arising in a variety of organs and tissues are the principal late somatic effects of radiation exposure. Organs and tissues differ greatly in their susceptibility to cancer induction by radiation; the major sites of cancer induced by whole-body radiation are the breast in women, the thyroid, hematopoietic tissues, the lung, and some digestive organs. It may be necessary to add skin cancer to the list of radiation-induced cancers for which tables are constructed.[61]

The Working Group has decided that only a selected group of organ and tissue sites can be characterized sufficiently for constructing radioepidemiologic tables. Because the epidemiologic characteristics (e.g., natural incidence, type and site of origin of neoplasm, age, and sex) vary widely among potentially radiation-induced cancers, one criterion for inclusion in the calculations of assigned shares is sufficient epidemiologic evidence for the radiation origin of the cancer to be inferred on the basis of a statistical excess above the natural incidence.

Past analyses of the available epidemiologic data have not consistently used specific criteria for precision and reliability of estimates to determine whether cancers should be considered inducible

by radiation. Furthermore, the Working Group did not lay out specific criteria for the quality of information needed to justify the presentation of assigned shares, although it does discuss the reasons for inclusion or exclusion qualitatively. The Oversight Committee recommends that the decision on whether to include specific sites of cancer in the tables of assigned shares be based, to the extent possible, on an evaluation of the reliability of the estimates, rather than on a subjective judgment preceding the data analysis. (Recommendation 3)

Recognizing that no criteria or analytic methods were yet available to carry out such tests, the Oversight Committee has assembled some thoughts on the choices. Pending the analyses suggested above, the criteria might be met for the following organ and tissue sites, on the basis of the cancer epidemiologic surveys indicated. The codes from the International Classification of Disease (ICD) are indicated.[75]

- Leukemia (ICD 9, 205-208), excluding chronic lymphocytic leukemia (ICD 9, 204)--Japanese atomic-bomb survivor survey; British ankylosing-spondylitis survey.

- Bone cancer (ICD 9, 170)--radium-dial painter studies; survey of German patients given injections of Ra-224.

- Thyroid cancer (ICD 9, 193)--Japanese atomic-bomb survivor survey; survey of radiation exposure of infants and children.

- Breast cancer (ICD 9, 174)--Japanese atomic-bomb survivor survey; chest-fluoroscopy patient surveys; postpartum-mastitis study.

- Lung cancer (ICD 9, 162)--Japanese atomic-bomb survivor survey; uranium-miner studies.

- Stomach cancer (ICD 9, 151)--Japanese atomic-bomb survivor survey.

- Colon cancer (ICD 9, 153)--Japanese atomic-bomb survivor survey; followup study of treatment for cancer of the cervix.

- Bladder cancer (ICD 9, 188)--Japanese atomic-bomb survivor survey; followup study of treatment for cancer of the cervix.

- Multiple myeloma (ICD 9, 203)--some evidence supporting inclusion from the most current Japanese atomic-bomb survivor survey and the Hanford nuclear-workers followup.

- Liver cancer (ICD 9, 155)--patients who received high-LET radiation from thorotrast, a contrast medium in x-ray diagnosis.

Calculations also could be developed for pancreatic cancer (ICD 9, 157); suggestive evidence has come from the current Japanese atomic-bomb survivor survey, the followup study of treatment for cancer of the cervix, and the Hanford nuclear-workers followup.

Epidemiologic evidence currently available does not clearly indicate that any of the following organ and tissue sites should be included in the calculations, but they could be analyzed for the reliability of their risk estimates:

- Salivary-gland cancer (ICD 9, 142).
- Esophageal cancer (ICD 9, 150).
- Gall bladder cancer (ICD 9, 156).
- Rectal cancer (ICD 9, 154).
- Malignant melanoma of the skin (ICD 9, 172).
- Other skin cancer (ICD 9, 173).
- Brain cancer (ICD 9, 191).
- Lymphoma (ICD 9, 200 and 202).
- Hodgkin's disease (ICD 9, 201).

Probably even less epidemiologic evidence is available to support inclusion of any of the following organ and tissue sites:

- o Cervical cancer (ICD 9, 180).
- o Uterine cancer (ICD 9, 182).
- o Kidney cancer (ICD 9, 189).
- o Ovarian cancer (ICD 9, 183).
- o Prostatic cancer (ICD 9, 185).

The Oversight Committee is, in general, in accord with the Working Group's choice of organ and tissue sites for estimation of assigned shares. The Working Group chose not to include multiple myeloma, but that choice is well within the uncertainties of current scientific information.

The situation regarding fetal (in utero) irradiation, however, deserves careful consideration. Concern has been raised that the relative-risk values (approximately 1.4 to 1.5) for leukemia in the relevant epidemiologic surveys are not large enough to warrant selection for the tables. However controversial the evidence may be, large risk coefficients have been derived for the first decade of life, and they are documented in such reports as those of UNSCEAR[70] and ICRP;[32] these cannot be ignored. Nevertheless, it remains unclear whether transition from a fetal condition to a postnatal condition should alter the leukemia risk coefficients so profoundly. In summary, the Oversight Committee finds the justification for the Working Group's decision to make the fetal leukemia risk coefficient identical with that of the first year of postnatal life to be weakly supported.

VI

SOURCES OF UNCERTAINTY

Section 7(b) of the Orphan Drug Act directs the Secretary of Health and Human Services to include "an evaluation which will assess the credibility, validity, and degree of certainty associated with [radioepidemiologic] tables." Although undoubtedly other interpretations of these three terms are reasonable, the Oversight Committee sees them as representing the following questions:

o Credibility: Do the tables as a whole portray to the scientific community a consistent, believable picture of radiation-induced cancer? Do the various assumptions required seem to fit together and relate easily to plausible mechanisms of cancer induction?

o Validity: Do the tables conform with observed risks of radiation-induced and other cancers where it is possible to observe them? Do any properties of the method seem to violate fundamental principles or empirical observations?

o Degree of Certainty: How good are the numbers in the tables? Are they biased in one direction or the other? Where do the uncertainties come from, how large are they, and how could they be reduced? What are the uncertainties in the information needed to use the tables? What are the consequences of the likely differences between the true assigned shares and those in the tables?

A. Nature of Uncertainties

In any scientific endeavor that attempts to organize information for a practical purpose, there are at least two sources of uncertainties.

First, uncertainties in data arise from an inability to make very precise measurements, because of inaccuracies in instruments or inherent variability in processes, or because the measurements have not been or cannot be made. The measurement or calculation of doses, either for deriving risk estimates or for estimating assigned shares for specific exposed people, is plagued by measurement uncertainties. Determining the number of cancers in a cohort may be a measurement problem, if the diagnostic techniques are imprecise; it is also subject to natural variation and will be substantially uncertain if the cohort is small.

Second, uncertainties in assumptions and methods used to analyze the data introduce additional uncertainties, often large and sometimes unsuspected. A model may fit the observed data in a narrow range--say, between 100 and 300 rads (1 and 3 Gy) for a specific type of cancer, but could be substantially in error elsewhere, because of inability to estimate coefficients precisely or misunderstandings about the nature of the physical, chemical, and biologic processes involved. The methods of analysis (Chapter III) and the assumptions used for projecting and extrapolating risks associated with radiation (Chapter IV) are all subject to such uncertainties.

In estimating an assigned share for a person who claims that his or her cancer was related to a specific radiation exposure, uncertainties may arise in specifying the circumstances of the individual exposure. To what kind of radiation was the person exposed, for how long, at what dose rate, resulting in what total dose? Was part of the total dose "wasted," that is, received after the initiation of the carcinogenic process? What were the relevant characteristics of the exposed person--age at exposure, age at diagnosis, nature of cancer, smoking history, and other risk factors? These are uncertainties in the information needed to use the tables and are beyond the control of the Working Group. The second group of uncertainties in the estimates of assigned shares come from those in the entries of the tables. We discuss the first class of uncertainties briefly in Section VI B and then turn to the second for the remainder of this chapter.

B. Information Needed to Use the Tables of Assigned Shares

Because the Orphan Drug Act specifies only that tables of probability of causation (assigned shares) should be devised, the Working Group has tended to concentrate on the problems of calculating the radiation risks, comparing them with nonradiation risks, and presenting the tables. Although it acknowledges the problems of determining the characteristics of a particular claimant that would affect his or her assigned share, the Working Group considers them outside its mandate and gives them less attention.

Several types of information about an individual claimant will be important, including:

1. Diagnosis of type of cancer(s) claimed as radiation-induced.
2. Total absorbed dose received by the organ or tissue in which cancer developed.
3. Dose rate(s) during exposure(s).
4. Radiation source and quality--external or internal, high- or low-LET, etc.
5. Age(s) at which dose(s) received.
6. Age at diagnosis of cancer.
7. Sex.
8. Smoking status.
9. Other risk factors--familial history of cancer or genetic predisposition, race, residence history, lifestyle (including dietary habits), and occupational or medical exposure to radiation or other carcinogens.

Items 1 to 8 are explicitly required for operation of the methods for determining assigned shares; the Working Group, by adopting the multiplicative-interaction model for other risk factors, assumes that none of the factors listed in item 9 would influence the estimates,

except possibly for the other radiation exposures (see discussion in Section III E).

Cancer diagnosis can be uncertain. For example, if a death certificate specified leukemia as the cause of death, it might be impossible to determine retrospectively whether it was chronic lymphocytic leukemia or some other variety.

With respect to dose, there is not only great uncertainty about individual doses (see also Section VI D 7), but a substantial chance for error through using the wrong measure of radiation exposure. If, for example, kerma rads in air are estimated for an exposed person and used to enter a table based on absorbed doses in tissue, overestimates of assigned share will likely result.

With respect to dose rate, the Working Group's method works best when dose rates are known to be lower than 5 rads/day, so that the response would always be in the linear region, or when dose rates are high enough for all the dose to be delivered in 1 day. In both cases, precise values of dose rate are unimportant. Uncertainties in dose rate might be substantial and important if, for example, fallout radiation totaling scores of rads but protracted over several days were asserted to be the cause of a cancer.

Radiation quality might be reasonably easy to determine, but it might be difficult to determine even whether internal sources were involved, let alone how much they contributed to specific organ doses.

The other characteristics in the list of eight (related to age and sex) are less likely to be mistaken. The characteristics in item 9 could be very uncertain, and these uncertainties would be very important <u>if the partition of risk factors included them</u>. As long as there is a socially or practically motivated decision not to include them in the partition, uncertainties about them for an individual claimant are not important.

The Oversight Committee believes that uncertainties in specifying the characteristics of an individual are important in deciding how or whether assigned shares should be used. Changing the risk factors to be included in the partition would also affect the uncertainty of the assigned shares calculated for a particular claimant. In passing legislation, Congress will need to be alerted to the problems created by uncertainty in the information needed to use the tables provided by the Working Group.

C. Magnitude of Uncertainties and Their Presentation

Now we turn to the uncertainties in the tables themselves, caused by uncertainties in the original data and by assumptions and methods used to convert them into estimates of assigned shares. Table VI-1 lists various sources of uncertainty. The users of the tables of assigned shares will need to appreciate the plausible magnitudes of changes in the tables that might occur when the uncertainties from these sources are resolved. For example, some work has already been done on the dosimetry for the Japanese atomic-bomb survivors, so some information on magnitudes of changes may be available. The fact that the Japanese atomic-bomb data are used to extrapolate to a U.S. population will concern many people. Some specific assumptions about shapes of dose-response relationships are made. The reader will ask what the magnitude of changes in the tables would be if other choices had been made.

In Chapter VII of its July 1984 draft report, the Working Group has tabulated the sources of uncertainty and discussed their importance in a largely qualitative fashion. Although a purely qualitative discussion might well give an adjudicator a sense of the accuracy and reliability of the tables, the Oversight Committee suggests that some quantitative assessment of uncertainties be conducted. Although quantification becomes more difficult as the uncertainties increase, the importance of communicating the potential consequences of the

TABLE VI-1

Selected Sources of Uncertainty in Constructing
Radioepidemiologic Tables

Uncertainties in Data

Which cancers should be accepted as radiation-inducible?

What is the effect of difficulties in the SEER data on the assigned-share estimates for cancer sites in which they are used?

How accurate are the cancer data in the Japanese and other studied populations?

How much difference will the revision in atomic-bomb dosimetry make?

Uncertainties in Assumptions and Methods

Is the constant-relative-risk time-projection method correct? Is the wavelike model correct for leukemia and bone cancers?

What errors can arise from the use of the latency assumption, with a standardized increase in the risk coefficients between 5 and 10 years?

Can the aggregate absolute risk over a period of observation be projected from Japanese to U.S. populations?

Should risk factors other than smoking be included in the partition? How well established are the multiplicative-interaction model for high-LET radiation and smoking and the additive-interaction model for low-LET radiation and smoking?

What is the range of possible error from the selected dose-response relationships?

Is the dose-rate adjustment adequate for all plausible exposure situations?

What is the effect of using the selected quality factors when the actual responses to high-LET radiation may be more complicated than those to low-LET radiation?

Are the selected quality factors consistent with the originally observed data for every cancer site?

uncertainties also increases. One way could be to provide a method for establishing a range of estimates, rather than a point estimate. The range could be established on the basis of known uncertainties due to poor data and could include the estimates of possible effects of choice of models and assumptions. Alternatively, the ranges could be established by sweeping the data and assumptions through their probable ranges in a sensitivity analysis and presenting some measure of the overall uncertainty observed in that process. The estimates could also be accompanied by text, formulas, and examples that would show how to generate uncertainty limits for various types of estimates.

The Oversight Committee recognizes the difficulties in quantifying sources of uncertainty (particularly the joint effects of a number of different factors, as emphasized above), but it believes that the Working Group could provide some indication of the range of error that might have been introduced by the assumptions it made. Some specific examples are presented later in this chapter.

D. Specific Sources of Uncertainty

In this section, the Oversight Committee summarizes its analysis of the uncertainties in specific parts of the Working Group's development of the tables of assigned shares. Our analysis is more qualitative than we wished; for selected uncertainties, we have attempted simple quantitative sensitivity analyses. These analyses should be considered as showing plausible uncertainties in assigned shares, rather than as rigorous analyses; they apply only to the specific examples selected and cannot be generalized. The subjects are discussed in the same order as in Chapter VII of the Working Group's report and with the same titles.

1. Sites of cancer and cell types

The Committee agrees with the Working Group that the available evidence for many sites and cell types is inadequate to establish or

deny the carcinogenic effects of radiation. Section V B discusses the problem of site selection for the tables. Except for chronic lymphocytic leukemia, which the Working Group excludes as demonstrably not induced by radiation, other sites are excluded for lack of sufficient positive evidence. Those exclusions, reasonable given the state of current knowledge, represent uncertainty and pose a dilemma regarding the disposition of cases in which radiation is claimed to have caused a type of cancer, such as multiple myeloma, for which assigned shares are not tabulated.

The Oversight Committee notes that the "leukemia excluding CLL" (leukemia excluding chronic lymphocytic leukemia) category is defined by exclusion, rather than inclusion. That is, it appears to be applicable to any case of leukemia that is not diagnosed as chronic granulocytic, acute, or chronic lymphocytic. The former two types have separate tables, and the latter is considered not to be induced by radiation. The definition could result in the inclusion in this category of some cases of chronic lymphocytic leukemia that are not specifically diagnosed as such. The benefit of the doubt is thereby given to incompletely diagnosed cases. If this judgment is deliberate, it should be acknowledged by the Working Group. Otherwise, the Working Group should consider redefining the category to embrace only miscellaneous leukemias that are probably inducible by radiation. (Recommendation 2)

The Committee is not aware of any others tumors for which different cell types imply a different probability of being induced by radiation. However, such differences may exist, and the possibility that separate tables may be needed in the future should be kept in mind. In some rare cancers or cell types, nearly a 100% share for radiation induction could be reasonably assigned--for example, in some cases of carcinoma of the mastoid, as seen in radium-dial painters.

2. Source tables of cancer incidence in the U.S. population

In Chapter V, we cautiously agree that SEER source tables[76] should be used. Furthermore, because the Working Group has adopted the relative-risk time-projection model and the multiplicative-interaction model in most circumstances, variations in cancer incidence in different parts of the United States or variations with risk factors for specific individuals would have no impact on calculations of assigned shares. Thus, the importance of the accuracy of the SEER tables is confounded with the uncertainty regarding those two assumptions. The baseline incidence rates in the most recent SEER tables may not be the most appropriate for assessing a particular case of cancer after a particular dose of radiation, particularly for a cancer like lung cancer, for which rates have changed and will continue to change. Similarly, it is not clear what period of baseline cancer rates should be used when projecting risk estimates derived from Japanese data to the risks in the U.S. population.

3. Latent period

As discussed in Section IV A 2, the Working Group has made several strong assumptions regarding the period from exposure until the observation of cancer. For cancers that occur earlier than at the end of the stated minimal latent period, assigned shares will be estimated as zero, whereas in some cases the unusual appearance of a cancer at an early age might suggest that it was in fact induced by radiation. However, 5 years may be an implausibly short latent period for other cancers or other ages at exposure, and cases of, say, breast cancer appearing between 5 and 15 years after exposure at age 15 may receive erroneously high assigned shares. Even if the risks rose smoothly between 5 and 10 years according to the assumed cubic smoothing function, the stepwise approximation would give the same assigned share to people who had been irradiated 7.01 and 7.99 years before their cancers were diagnosed. If the cubic function were exactly correct, the factor to be applied to the relative-risk coefficient would be

about 0.37 at 7.01 years and 0.63 at 7.99 years, compared with 0.5 assigned to both according to the stepwise interpolation formula. The uncertainty introduced by the formula is thus about ±26%; the "error" in assigned share would be relatively lower, depending on its value for a particular case.

Moreover, if a different but plausible cubic function were assumed--for example, over the period 5 to 15 years after exposure--the risks in the period 5 to 9 years could change by a factor of over 2. Specifically, the Working Group's T factor at 7 years would change from 0.5 to about 0.21 and at 9 years from 0.93 to about 0.44. An assigned share of 20% would change to about 9.5 and 10.5%, respectively.

4. Coefficients describing the dependence of risk on dose

The Working Group has drawn attention in its Chapter VII to the statistical uncertainties in the risk coefficients derived from the Japanese atomic-bomb survivor study and correctly points out that, in the Kato and Schull mortality study,[38] only for leukemia is the 90% confidence interval for absolute risk less than a factor of 2. Uncertainties in the absolute excess risk are proportionally reflected in the relative-risk coefficients the Working Group derives from them. If an assigned share of 20% were derived from these coefficients, and the true value of the coefficient were twice or half its nominal value, the assigned share would rise to 33% or fall to 11%, respectively. Risks for a particular age group will in general have a considerably greater range of statistical uncertainty because of the smaller number of cases on which the risk estimates are based.

Although our interim report supported the use of the linear-quadratic dose-response model, the possibility that consideration of available data should be more detailed to permit more precise determination of risk coefficients was implicit in our recommendation. The Working Group has indicated that it is unable to do that. The Committee is therefore concerned over the degree of uncertainty that

has been introduced by the Working Group's adoption of a unique dose-reduction factor applied to the risk coefficients from the BEIR III report.[50] The factor of 2.5 was initially derived for leukemia and was somewhat arbitrarily applied by the Working Group to most solid tumors. Uncertainty exists as to whether a dose-reduction factor of 2.5 in moving from linear to linear-quadratic coefficients is indeed appropriate at low doses for most solid tumors and whether the 116-rad (1.16-Gy) crossover dose for a linear-quadratic model should be applied universally to those cancer sites. Indeed, it seems likely that, if the relevant data were available, the appropriate dose-reduction factor would vary substantially with cancer site.

The Oversight Committee agrees that it may be difficult to determine the degree of uncertainty introduced by adopting the risk coefficients translated from BEIR III by the Working Group, rather than using some other method of analysis. Nevertheless, the uncertainty must be considerable. Even if the coefficients were accurate for the selected model, the choice of model introduces uncertainties. The difference between linear and linear-quadratic models varies with dose. If the linear-quadratic model produces an assigned share of 20%, the linear model would produce 36.5% at 10 rads, 34.8% at 20 rads, 30.4% at 50 rads, 25.1% at 100 rads, and 18.7% at 200 rads. The factor of increase varies from 1.83 at 10 rads to 1.0 at 174 rads; there is a decrease in assigned share for higher doses.

Some of this uncertainty can be removed in future revisions of the tables, by combining longer followup from Japan, recalculation of doses to the Japanese, and results of other radioepidemiologic studies. (Recommendation 12)

5. Influence of age at exposure

As implied by the mandate in the Orphan Drug Act, age at exposure is a particularly important variable for the estimation of assigned shares, especially for some specific cancer sites. As noted in Section

VI D 4, the statistical uncertainties in the risk coefficients based on all age groups and both sexes in the Japanese atomic-bomb survivor data are increased when the data are separated into several age groups or by sex. The standard error decreases as $1/\sqrt{N}$, where N is the number of cancer cases. The uncertainty will generally be larger for the younger age groups, in which fewer cancer cases have as yet been observed, and smaller for the older age groups. The average increase would be about a factor of 2 if there were four age groups. The influence on assigned shares would be somewhat smaller, depending on the value of assigned share. As discussed in Section V B, use of the BEIR III coefficients forces a coarse stratification of risk coefficients by age at exposure and sometimes forces adoption of factors from BEIR III that appear to be better known today than they were when the BEIR III estimates were developed in 1979. Looking at age at exposure as a continuous variable might give different answers for assigned shares as a function of other variables as well (see Sections III D and VI E). The Working Group deals with the coarseness of the stratification by interpolating the risk coefficients with a fixed formula. The Oversight Committee supports the idea of a smooth variation with age at exposure, but cannot assess the uncertainty introduced by the choice of the interpolation formula.

6. Sex

The Committee agrees with the Working Group that the quantitative differences in radiation-induced cancer between the two sexes are uncertain. An additional uncertainty exists about differences between Japan and the United States in sex-specific incidence rates. Thus, translation of estimates of risk from Japan to the United States might have to be dealt with differently for the two sexes. However, it is unclear what effect this treatment could have; we emphasize only that there is an additional uncertainty factor that cannot yet be reduced in the calculations.

7. Dosimetry

Two sources of uncertainty in relation to dosimetry should be clearly distinguished. The first uncertainty, as indicated in Section VI B, is in estimating appropriate doses for individuals to calculate their assigned shares. Location-based and areawide estimates of exposure must often be used to estimate individual doses, and great uncertainty over the applicability of these estimates to individuals must occur both in relation to fallout and in relation to individual exposures in uranium mining. For example, not only may area measurements within mines be inapplicable to individual uranium miners, but the extent to which cumulative doses should be counted in estimating assigned shares is also uncertain. If the assumption regarding the minimal latent period is correct, radiation exposures in the last few years before diagnosis of the relevant cancer cannot have contributed to the induction of the cancer, although they might have contributed to its promotion. This observation has led to the concept of "wasted exposure"; some of the total dose up to diagnosis of the cancer probably should be discounted in calculating assigned shares for individual uranium miners. Nevertheless, the correct time for which this discounting should be done is uncertain.

The other source of uncertainty in relation to dosimetry has to do with the estimation of radiation risks. Even if the estimates are unbiased, uncrtainties in dose estimates tend to result in under-estimates of radiation effects, because the dose estimates are bounded (by zero) on the low side but are unbounded on the high side. If the dose-response function is truly curvilinear, errors in dose estimates also tend to distort its shape.

Specifically, the dosimetry of the Japanese atomic-bomb survivors is in doubt, and the risk coefficients derived from their experience are similarly uncertain. The Hiroshima and Nagasaki populations are by far the most important source of information on radiation risks, because of the range of doses received and because data are available

on both sexes and all ages. Until recently, doses had been calculated by a procedure known as the T-65 dosimetry. As mentioned earlier, an effort is underway to reestimate the doses with more precise calculations of gamma-ray and neutron fluxes from the bombs, augmented by novel ways of reconstructing doses that use thermoluminescence of residual excited atoms in ceramic materials still in their original locations or induced activity in electric powerline insulators.[57] This effort is nearing completion. If the change in doses caused risk coefficients to rise by a factor of 2, an assigned share of 20% would increase to 33%. Additional years of cancer incidence are now available for this population; reanalysis of the cancer incidence data with the new doses is not expected to be completed until 1985.

The risk estimates made by the Working Group are based on a mixture of studies involving both whole- and partial-body exposures. These estimates are assumed to apply whenever an organ receives a specified dose, irrespective of the exposure of other parts of the body. In some tissues, the error introduced by that assumption will be small; for leukemias, however, the fraction of the entire bone marrow irradiated is thought to be important.

8. Dose-response function

Chapter IV discusses the controversy over the appropriate functional form for the dose-response relationships for different cancers under different conditions of exposure. Some observers will see reasons why the Working Group should have adopted a linear relationship for, say, stomach cancer, whereas others will object to the linear assumption for breast cancer. Whatever the true relationships turn out to be, our current appreciation of them is clearly uncertain.

We illustrate the possible uncertainty in relation to the two sites mentioned above. For stomach cancer, the Working Group's first example (on p. 216 of its draft), if based on the assumption of a linear

dose-response function, would result in a calculated assigned share of 16.5%, rather than the 7.9% resulting from the linear-quadratic dose-response function assumed. For breast cancer, however, the Working Group's examples are based on the assumption of linearity. Our calculations suggest that, if the first two examples were based instead on the assumptions of a linear-quadratic dose-reponse function, the first calculated assigned share would be reduced from 14% to 6.5%, and the second, from 1.5% to 0.6%. All these differences can be derived from the factor of 2.5 applied by the Working Group to the BEIR III linear risk coefficients. It is commonly assumed that the factor of 2.5 adequately characterizes the uncertainty in dose-response relationships for radiation, but other functional forms could in principle prove correct with greater differences from the Working Group's estimates of risk for low doses.

9. Dose rate

The approach used by the Working Group in relation to dose rate is unusual, but probably workable in most situations. However, because of the way it has treated different elements of dose, effectively in subdoses of up to 5 rads (0.05 Gy) when exposure is protracted, calculations are usually applied at the low end of the dose-response function. Although that is compatible with the presumption that effects are lower at low dose rates than at high dose rates (a presumption with which we generally agree), it nevertheless results in a computation of risk different from that if dosages were allowed to accumulate and calculations of assigned shares were based on a single cumulative dose, rather than on different subsegments of dose. With the linear-quadratic dose-response model, the increase in assigned share for small doses delivered in the same year and treated as a single cumulative dose is small. For example, the difference is only 15% between the risks from 10 2-rad doses during 1 year treated separately and treated as a single 20-rad dose. However, the difference in risk between 50 2-rad doses and a single 100-rad dose is 83%. Such a comparison would be further complicated if the protraction

of dose extended over periods long enough for the dependence of risk coefficients on age at exposure to be felt.

10. Time-response models

The Working Group has adopted constant-relative-risk models for most cancer sites in its computations for the variation in risk with time after exposure. That coincides with the approach recommended in our interim report. However, the approach cannot be verified for times after exposure longer than those on which data are available. Table VI-1 on p. 97 of the Working Group's draft report indicates that data are not available on the period beyond 35 years after first exposure for any site and that most coefficients are based on observations spanning no more than 30 years after first exposure.

If the true time-response model is not the one the Working Group assumes for a particular cancer, differences in the assigned shares will result. The constant-relative-risk model produces assigned shares that do not vary with time after exposure. A constant-absolute-risk model will produce assigned shares that generally decrease with time after exposure, because baseline risks usually increase with age. The wavelike model used for leukemia and bone cancer produces assigned shares that decrease even more rapidly. These models are also sensitive to the selection of mean and variance in the log-normal distribution of risk with time after exposure. Differences in assigned share among various models can be a factor of 3 even for times after exposure less than the period of observation for the underlying epidemiologic study and can become larger thereafter.

Consider a male with cancer of the stomach diagnosed at age 55 after irradiation at age 25. Suppose the Working Group calculates that his assigned share is 20%, based on their $K(25,m) = 0.00383$. This assigned share would be independent of age after age 35. The dose that would produce this share is approximately 47 rads. If we used a constant-absolute-risk model, the excess incidence is 0.0308 per rad

per 100,000 people per year (Working Group Table VI-1). At age 55, the baseline incidence is 24.1 per 100,000 people per year (Working Group Table VI-2). The relative-risk ratio under the constant-absolute-risk model would be 0.0308 F(47)/24.1 = 0.0834, and the assigned share approximately 7.7%. At age 35, when the baseline incidence is only 2.1 per 100,000 people per year, the assigned share is approximately 49%. The potential uncertainty is thus about a factor of 2.5 in this example, without going beyond 30 years after exposure.

11. Other sources of uncertainty

The Working Group's discussion under this title focuses on risk factors for cancer that could affect either the baseline risk of cancer or the susceptibility to the carcinogenic effects of radiation. Knowledge of such factors might permit us to develop a finer partition for the tables of assigned shares to take them into account. In some ways, the estimate assigned to an individual might become more appropriate if these factors are taken into account. However, adding a risk factor to the partition does not affect the accuracy of the assigned share estimated for the coarser partition, because it was calculated for the group of people to which the person was assigned in that coarser partition and is not a property of the person.

Another uncertainty is introduced by the need to make an assumption about how radiation-related risks transfer from one population to another. The Working Group assumes that the absolute excess in Japan will apply in the United States, no matter how the baseline incidence rates may differ. If it proved better to transfer relative risk coefficients from Japan to the United States, the coefficients used for assigned shares would decrease when the Japanese baseline was greater than the U.S. baseline and increase when it was lower. Appendix B shows that an assigned share of 17% calculated from a relative risk in Japan of 1.2 could rise to 44% or fall to 5% if the baseline risks differed by a factor of 4 and the relative risks were transferred instead of the absolute risks.

12. High-LET Radiation

We have indicated in several places that the Working Group's treatment of effects of high-LET radiation--specifically, alpha radiation as related to uranium miners--needs further work. The use of a uniform quality factor to adjust the dose before entering the tables will work well only for a relatively narrow range of doses and few cancer sites. Moreover, the value of the quality factor would be uncertain, even if the concept were correct. An uncertainty factor of 2.5 is introduced by the need to interpret the ICRP methods for deriving the quality factors. For neutrons, the new Japanese dosimetry may show that we know less about the carcinogenic effectiveness of neutrons for humans than we thought we did. These uncertainties are essentially independent of most other uncertainties and will tend to compound the ones in the assigned shares for low-LET radiation.

13. Summary

In summary, the sensitivity analyses presented earlier in this section show the following variations in assigned shares:

o Dose-rate effect. If no dose-rate adjustment were applied, risk estimates could increase by up to 2.5 times. For 20 rads treated as a single dose, instead of protracted, risk would increase by 15%; an assigned share of 20% would change to 22.3%. For 100 rads treated as a single dose instead of protracted, risk would increase by 83%; an assigned share of 20% would change to 31.4%.

o Dose-response model, L vs. LQ. Adoption of a linear dose-response model for all cancer sites (in addition to breast and thyroid), instead of a linear-quadratic model, would increase assigned shares, depending on the dose. An assigned share of 20% would change to 36.5% at 10 rads and to 25.1% at 100 rads.

o Latent-period smoothing function. Adoption, for example, of a cubic function for the period 5 to 15 years after exposure (instead of 5 to 10 years) would change an assigned share of 20% to about 10% for cancers occurring 5 to 9 years after exposure.

o Sampling errors in epidemiologic data. Errors in absolute-risk coefficients estimated from Japanese atomic-bomb survivor data confer errors in assigned-share values that could reduce or increase them by a factor of 2. For example, an assigned share of 20% would be reduced to 11% or increased to 33% if the true risk estimate differed by a factor of 2 from that estimated.

o New Japanese dosimetry. If the doses decreased by an average of a factor of 2, with no other changes, risk estimates would rise by a factor of 2 and an assigned share of 20% would increase to 33%.

o Time-response model. If the constant-absolute-risk model were used instead of the constant-relative-risk model for stomach cancer, assigned share for 10 years after exposure would increase by factor of 2.5, whereas assigned share for 30 years after exposure would decrease by factor of 2.5, when assigned share with constant-relative-risk model was about 20%.

o Transfer of risk coefficients from Japan to United States. If transfer of relative-risk coefficents instead of absolute-risk coefficients were used for a cancer with 4 times the baseline incidence in the United States as in Japan, an assigned share of 17% would change to 44%; if the baseline incidence were a quarter, it would change to 5%.

E. Uncertainty Suggested by a Sensitivity Analysis

To investigate further the possible extent of uncertainty in assigned shares stemming from choices of data, assumptions, and methods, the Oversight Committee computed assigned shares through a

different type of analysis from that used by the Working Group, starting with mortality data on the atomic-bomb survivors. Several different models of radiation carcinogenesis were used, and the results were compared. This section discusses the implications of that comparison for the uncertainty that may exist in the tables as a result of decisions on how to approach the task. The Committee emphasizes that the results are sensitive to those choices.

The choice of underlying model for the probability of developing a specified type of cancer during the next year--given age at exposure, years since exposure, sex, and the particulars of the dose--is uncertain and subject to debate. It is important to assess the consequences of different choices. Furthermore, the sensitivity of the results to those choices may well depend on the range of values of the determining variables over which the comparison is made; the agreement among different estimates may be satisfactory in a narrow range, but not elsewhere. Whether the range is wide enough depends on the uses to which the tables are put.

The assigned share depends on the ratio of the probability of developing cancer after exposure to dose d to the probability after exposure to dose zero:

$$AS = R/(1 + R) = [h(d) - h(0)]/h(d) = 1 - h(0)/h(d), \qquad (VI-1)$$

where $R = [h(d) - h(0)]/h(0)$ is the excess for the exposed population relative to the unexposed population and $h(d)$ is the hazard rate at dose d with all other variables fixed. Clearly, the shape of AS as a function of dose and of the other variables depends on how fast $h(d)$ increases, compared with the value of $h(0)$, the hazard at dose zero. Thus, it depends on how the hazard <u>changes</u> with these variables, rather than on the hazard rate itself. For example, if $h(d)$ increases rapidly with d, then AS will be large for relatively small doses. The effect of a small increase in $h(d)$ is magnified if $h(0)$ is also small. Assigned shares may thus be large when radiation has a strong effect in

causing an unusual cancer type. The alternative models evaluated here are very different from one another and from the model based on modified BEIR III coefficients as used by the Working Group. They differ in how they depend on dose, age at exposure, sex, and so forth. We would like to compare the consequences of these differences and also to compare the results with the available observed data.

Unfortunately, the most extensive of the available published data, referring to the atomic-bomb survivors,[56] are only for mortality in a Japanese population. The Working Group uses coefficients from BEIR III that at least nominally apply to incidence and adjusts them for use in a U.S. population. It is well known that incidence rates are higher than mortality rates, unless fatality rates approach 100% for a specific cancer, and that rates are not the same in Japan as in the United States--again depending on the type of cancer. But for both rates, it is the relative ratio, h(0)/h(d), that concerns us. Therefore, the actual differences between incidence rates and mortality rates are of much less import.

For three types of cancer (stomach, for which there are the most data; breast, for which the Working Group uses an updated linear rather than a linear-quadratic model; and colon, as a further check), we have computed estimated mortality rates under many sets of parameters for 15 models and used them to compute tables of assigned shares. Because our source data on radiation exposure were reported as rads kerma, divided between gamma and neutron radiation, we report those values on our plots.

The different models provide a multitude of results that can be quite different from each other. The Oversight Committee had originally intended to compare these results also with those of the Working Group. Because the Committee's analyses necessarily used rads kerma, instead of absorbed dose in tissue, a conversion would be required. Moreover, although assigned shares for mortality are expected to be similar to those for incidence, they are not expected to

be identical. For these reasons, the corresponding results of the Working Group are discussed briefly but are not plotted.

For each type of cancer, we have selected the same typical set of cases to plot, insofar as they are available, to provide a visual comparison. Assigned share is on the vertical axis (in percent) and age at exposure (which is age at time of bombing) is on the horizontal axis. The Working Group does not show different plots for different ages of diagnosis, because it assumes a constant-relative-risk model, but we have drawn curves for each of three ages at time of death--37.5, 50.0, and 73.0 years--for each model. Age at time of death is restricted for any given age at exposure, because the atomic-bomb survivors have been followed in the published data only from 1950 to 1978. Thus, the curves for age at time of death are drawn only for the regions of age at exposure where the data are most frequent. When the age at time of death is 50 years, the reliable range for age at exposure is 27 to 42 years. When the age at time of death is 37.5 years, the corresponding range for age at exposure is 14.5 to 27 years, and when the age at time of death is 73 years, the range for age at exposure is 42 to 65 years. These three choices of age at time of death thus produce non-overlapping reliable ranges for age at exposure, which is convenient for plotting the results.

When the three zones for different ages at time of death do not join smoothly, the corresponding plots show an influence of age at time of death, and the size of the discontinuity reflects the importance that the model assigns to that variable (Figure VI-1). Although the effect of the discontinuity is usually smaller, dying 15 or 20 years later can reduce the assigned share by as much as 10%, e.g., from 25% to 15%.

The Working Group plotted its results on a semilogarithmic scale, presumably to separate the curves for different sexes and doses at low values of assigned shares. We chose to plot our comparisons on an arithmetic scale (rectangular coordinates), to emphasize the

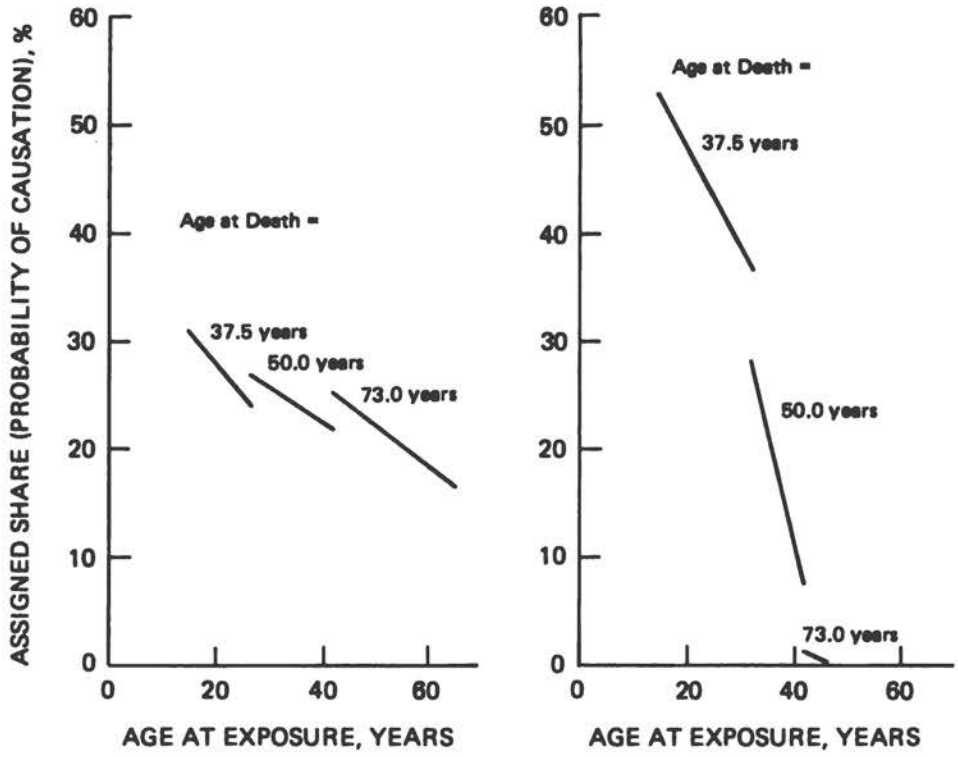

FIGURE VI-1 Influence of age at death. Plots of assigned share versus age at exposure show discontinuities corresponding to different ages at death from cancer. Left, breast cancer in females for 18.5 rads gamma and 3.3 rads neutron (kerma) with Model 5. Right, stomach cancer in females for 214.4 rads gamma and 29.2 rads neutron (kerma) with Model 5.

similarities and differences in the region above 10%, where they will be most important for compensation decisions. Results are presented for two levels of total rads kerma--21.8 (G = 18.5, N = 3.3) and 243.6 (G = 214.4, N = 29.2), used because they were observed and published in the available atomic-bomb survivor data. (The equivalents in grays are 0.218, 0.185, 0.033, 2.436, 2.144, and 0.292, respectively.)

Our analyses can be used to investigate the differences in assigned shares that result from constraining the models in various ways. Model 1 is a very general model allowing both linear and quadratic terms in

the gamma kerma, a separate linear term for neutron kerma, an effect of age at exposure, an effect of age at death, and an effect of the sex of the affected person. (See Section III D and Appendix D.) Interactions among these terms are also permitted. Model 5 is similar, but only the total kerma (neutron plus gamma) is used. In model 8, there is no quadratic term and no third-order interaction. The effects are estimated by a maximum likelihood fit, using the logistic model with published mortality data from 1950 to 1978.

The mortality rate for zero dose is observed in a special sample of the Japanese population not exposed at the time of the bombings; it is sometimes greater than that for the people who received low doses from the bombs. It also happens that the coefficient of the quadratic term in kerma and some of those for the interaction terms are often estimated to be negative. For these reasons, although all the mortality rates are positive, the estimate of h(d) can be less than the estimate of h(0), so that the estimated assigned share appears to be negative. Such values need not be interpreted as a beneficial effect of radiation, because the zero-dose data are unreliable. Therefore, the corresponding curves are not plotted for the specific parameters and specific choices of model for which the assigned shares are estimated to be negative, which the Committee considers unrealistic.

Figure VI-2 shows that the overall results differ among the various models. In the case of men exposed to high levels of radiation (243.6 rads kerma) at ages between 28 and 42 years and dying of stomach cancer at age 50, the differences are small (left side of Figure VI-2). More commonly, they can be substantial, as in the case of women exposed to lower levels (21.8 rads kerma) and dying of breast cancer at age 50 (right side of Figure VI-2).

The effect of radiation on the value of the assigned share appears to depend on age at exposure. In Figure VI-3, we plot assigned share against age at exposure for stomach cancer in females. If we compare the plot on the left for 21.8 rads kerma with the one on the right for

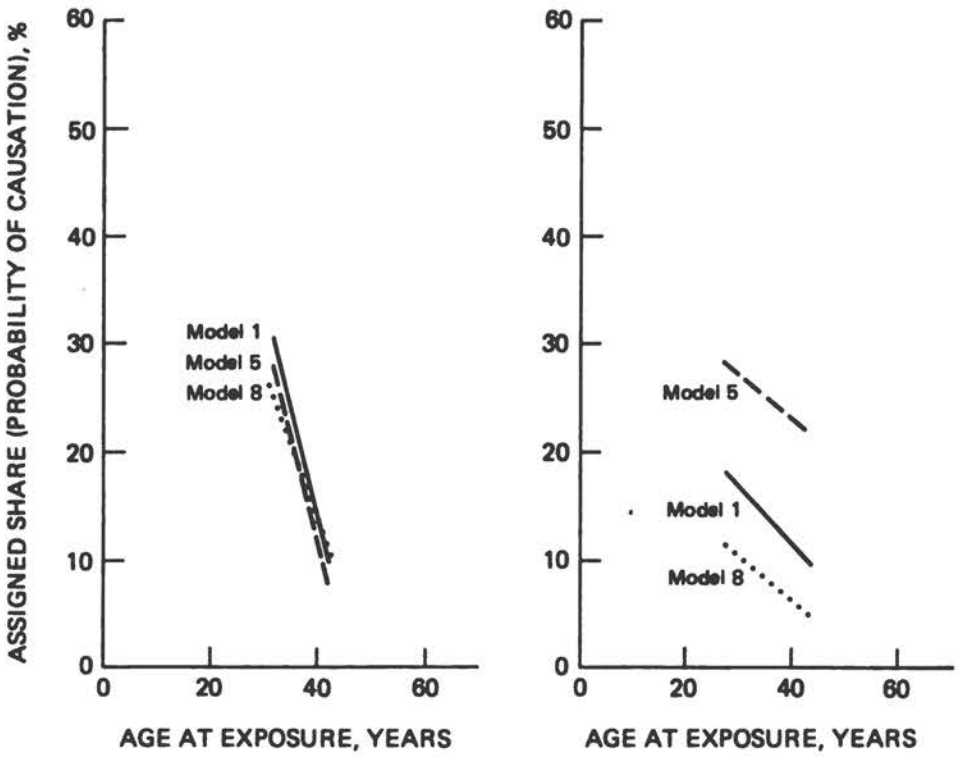

FIGURE VI-2 Influence of model. Plots of assigned share versus age at exposure show that results in narrow range (age at death from cancer, 50.0 years) can be insensitive to choice of model, as on left--stomach cancer in males for 214.4 rads gamma and 29.2 rads neutron (kerma)--or very sensitive to it, as on right--breast cancer in females for 18.5 rads gamma and 3.3 rads neutron (kerma).

243.6 rads kerma, we find a strong radiation effect in women exposed at age 20, but no effect in women exposed at age 60; in fact, the estimated assigned share is nominally negative for the higher radiation level. All of the plots exhibit strong effects of age at exposure and of sex.

In conclusion, the uncertainties introduced by the choice of model can be severe, but are not always. Furthermore, the effects of changing parameters seem to be important and different from what was expected by the Working Group. In the case of stomach cancer, the assigned shares estimated from any of the models suggested are lower by

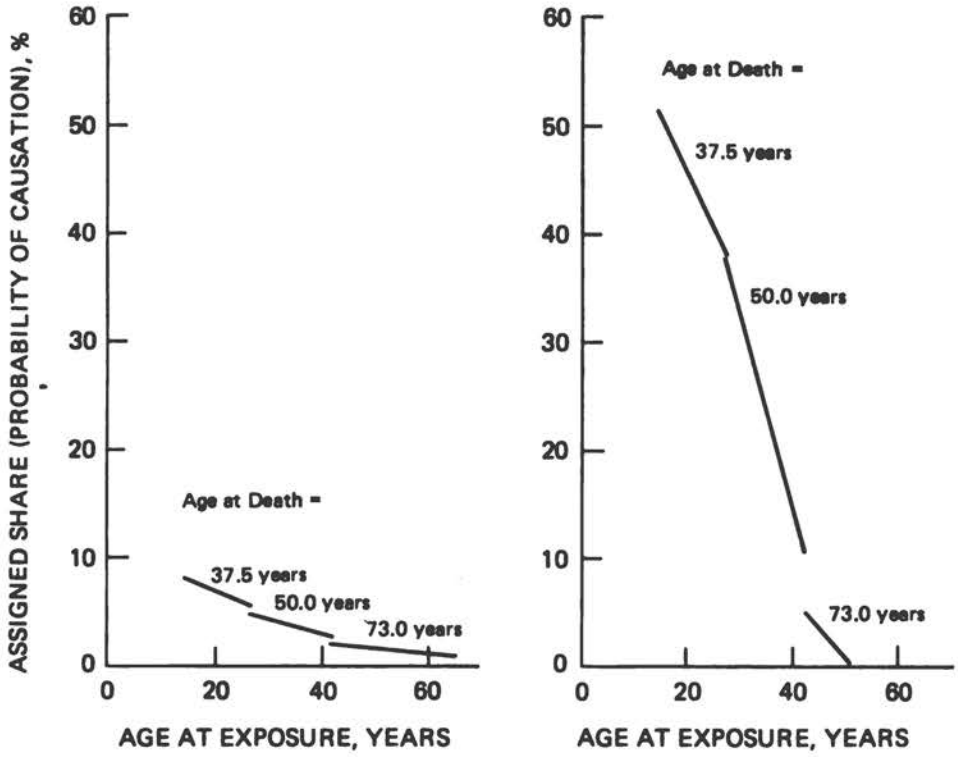

FIGURE VI-3 Influence of radiation. Plots of assigned share versus age at exposure show that effect of radiation is pronounced at early age of exposure but less so later in life for stomach cancer in females. Both plots are for Model 1. Left, 18.5 rads gamma and 3.3 rads neutron (kerma). Right, 214.4 rads gamma and 29.2 rads neutron (kerma).

a factor of 2 to 6 or more than those obtained by the Working Group. These differences seem too large to be explained by conversions from rads kerma to absorbed dose or by differences between incidence and mortality. In contrast, the Working Group's results for breast cancer fall in the same general range as do those from the various logistic models. Here the Working Group used a linear dose-response model and more recent data. The agreement between the two approaches is also better for colon cancer than for stomach cancer, even though the assumptions and data currency is the same for the two sites. Clearly, more study is needed, particularly using the new data from Japan expected to become available in the next 2 years.

The Oversight Committee recommends that the Working Group conduct and report on a quantitative appraisal, such as a sensitivity analysis, to evaluate the uncertainties in the assumptions, data, and methods used in constructing the tables; their influence on the reliability of the tables of assigned shares; and their implications for possible uses of the tables. (Recommendation 24)

VII

WIDER ISSUES

The formal charge to the Oversight Committee was to review the data sources, assumptions, methods, and means of handling uncertainty used by the Ad Hoc Working Group. In the course of their work, the members of the Committee developed some insights into how the radioepidemiologic tables were intended to be used and how they might be used or misused for other purposes. This chapter should be regarded, not as a comment on the report of the Working Group, but as supplementary material that may have value to those considering implementing the concept of assigned shares. It discusses some economic, social, and ethical issues that follow from the requirements of our charge, and it aims to alert Congress, the public, and other interested groups to possible unintended consequences, as well as to some problems with the current state of knowledge.

The topics discussed here are far from all-inclusive. The influence of uncertainties and changes in the tables with time is discussed first, because that topic is intermediate between considerations that are mainly scientific and within our formal charge and those which are policy-oriented and beyond it. The chapter then treats other issues, including the applicability of the tables and possible precedents set for carcinogens other than radiation, the potential implications of the tables for standards of protection for radiation hazards, and the compensation formulas and systems that might be used.

A. Influence of Uncertainties and Changes in Tables

Chapter VI laid out the sources of uncertainties in the estimates of assigned shares and discussed their possible magnitudes. This section first describes current uncertainties in the tables and their

implications. Next, it discusses how responses to the uncertainties and other circumstances will require the tables to change from time to time. Finally, it lays out the Committee's thoughts on the consequences for compensation decisions of the current uncertainties and anticipated changes in the tables.

1. Current Uncertainties

As discussed in Chapter VI, the Oversight Committee suspects that the uncertainties in data, assumptions, and methods used in the estimation of assigned shares are substantial. Unless the sensitivity of the assigned shares to these uncertainties proves to be far less than the Oversight Committee suspects, the tables will prove correspondingly uncertain. Undoubtedly, the relative uncertainty differs according to type of tumor, dose, characteristics of the exposed population group, and the absolute magnitude of the assigned share. Our limited investigations have shown that the use of different reasonable assumptions or methods can produce estimates of assigned share that differ by a factor of 2, 4, or more from the Working Group's estimates when the latter are near 20%. Considering all sources of uncertainty, assigned shares may often be substantially misestimated, and the overall reliability of the tables might be a focus of controversy in any claim for compensation.

For example, it may be possible to estimate that the assigned share is 20% for a particular situation and to conclude that that is the best current scientific estimate of the true probability. But the uncertainty may be so great that the true assigned share could be 80% or 5%, and any tribunal that awards compensation will have to wrestle with the problem of settling claims when faced with such uncertainties.

It is possible that even very uncertain tables could be useful in an environment where conflicting assertions by expert witnesses seem to imply even greater uncertainty. The Oversight Committee has not investigated the relative merits of the assigned-share approach and the

tort-law approach sufficiently to make a recommendation, nor was it asked to do so. Nevertheless, the uncertainties in the tables have various implications. One possibility is that both plaintiff and defendant would argue that the assigned share for the claimant was not correct and that the upper or lower bound of the range of uncertainty should be used in the decision. Avoidance of this controversy may have been the intent behind the language in the Orphan Drug Act (PL 97-414) that specifies that the tables shall contain single numbers, rather than ranges. But to avoid discussion of uncertainties in a quantitative fashion may suggest to nonscientists an unrealistically high precision of scientific knowledge. The mere existence of tabulations of assigned shares, especially without accompanying quantitative expressions of their uncertainty, could stimulate unintended uses--scientific or otherwise--that would be inappropriate, given the actual state of uncertainty. Publication of tables that must be changed markedly in a matter of a few years may damage the credibility of an otherwise valuable concept. Alternatively, publication of the tables may be the very stimulus needed to improve the scientific basis for estimating radiation risks and corresponding assigned shares.

2. Changes in Tables with Time

Congress has anticipated the need for the radioepidemiologic tables to change with time and has mandated in the Orphan Drug Act that they be updated every 4 years or more often. The Oversight Committee notes that at least three circumstances may necessitate periodic revision of the tables: changes in population rates of cancer incidence and mortality, changes in scientific knowledge (which may occur through several lines of progress), and changes in the partition that specifies the risk factors to be considered in estimating assigned shares. The first circumstance could be accounted for by automatic revisions produced within the system. The second would require periodic scientific review. The third would require revision in response to the changing framework for the use of the tables.

a. Changes in Population Rates

Chapter V points out that the rates for some types of cancers are changing and that in recent years there has been an indication of increased incidence of some of those, possibly largely because of increases in the efficiency of cancer registration. However, rates are rising rapidly for some sites, such as lung cancer (particularly in women), whereas rates appear to be continuing to decrease for some other sites, such as stomach cancer in both sexes. Many claims filed against the government for cancers observed years or even decades ago have not been settled. Other claims may yet be filed for cancers arising in the 1950s, 1960s, and 1970s. If the radioepidemiologic tables are to be used in settling those claims, assigned shares will have to be calculated for the cancer victims. A person's assigned share will depend on the appropriate selection of a comparison incidence rate, unless the underlying model applied in developing assigned shares reflects a multiplicative relationship between radiation and risk from all other causes. If a multiplicative relationship is assumed, changes in baseline incidence rates are not important in the calculation of assigned shares. For some sites, however, risks may not be multiplicative, and it may be essential to use the appropriate baseline rate in determining the assigned share. Ideally, the appropriate baseline rate is that which occurred in the population in the year that the individual's cancer was diagnosed. For such sites, therefore, tables of assigned shares may need to be revised regularly, possibly even annually, with their values depending on the year of diagnosis. This procedure, although it requires repeated production of tables, is not complex and would be considerably simplified if the algorithms for producing the assigned shares were programed for computer implementation.

If tables are to be based on both incidence and mortality rates, they should take into account the significant increases in survival in the last decade for many cancers that previously had much lower survival rates, including some leukemias, Hodgkin's disease, breast

cancer, such childhood cancers as Wilms's tumor and possibly neuroblastoma, stomach cancer, colon cancer, and melanoma. Others, such as thyroid cancer, have displayed a relatively low fatality rate, irrespective of treatment. With sufficient data on radiation risks for mortality and incidence, the availability of both incidence and mortality baseline risks would provide a basis for more reliable tables.

b. Changes in Understanding of Radiation-Induced Cancer

Epidemiologic studies of irradiated populations continue to provide new data for risk estimation, and within a relatively short time (perhaps 2 years) this new information will require a reexamination of the radioepidemiologic tables. Such changes, if substantial, could cause confusion; some thought should be given to how changes in the risk estimates would be accommodated.

The changes anticipated to modify our understanding of radiation carcinogenesis in the next few years include changes in the estimates of the radiation doses in exposed populations, especially in the atomic-bomb survivors; new information on the incidence of solid cancers with longer followup in irradiated populations, including the atomic-bomb survivors; the use of improved methods for statistical analysis of the epidemiologic data; and new information on the mechanisms of radiation carcinogenesis.

The extensive program to reevaluate the dosimetry of the atomic bombs in Nagasaki and Hiroshima is nearing completion. It will probably result in changes in the doses of the survivors on which the current risk estimates have been based. Because the Japanese atomic-bomb survivors provide many of the data on which the tables of assigned shares are based, any substantial change in the doses could result in changes in cancer risk estimates and thus in assigned-share estimates.

Over 60% of the Japanese atomic-bomb survivors are still alive, and, because of the long latent periods for the appearance of solid cancers, much information on cancer incidence in this aging population

remains to be ascertained.[72] The situation is similar for other radioepidemiologic studies now in progress.[6] The new data will provide considerable insight about the response of human populations to radiation. Furthermore, the new Japanese dosimetry may make it possible to pool data from Hiroshima and Nagasaki appropriately, thereby providing a larger data base to allow a better definition of dose-response relationships for estimating carcinogenic risk, particularly in the low-dose region. Which cancer types should be included in the tables of assigned shares will also become clearer as the data for various solid cancers accumulate.

A number of other irradiated populations are under study.[6] In the long term, these studies may provide a basis of comparison for estimating the cancer risks that will be important for the refinement of the tables.

The accumulating data are also likely to be subjected to different and more informative methods of analysis. Statistical methods that are less sensitive to assumptions about the radiobiology of cancer and that examine more explicitly the functional dependence of risks on risk factors may be used (see Section III D for examples). These analyses should provide a better understanding of age dependence, sex dependence, and dose dependence of the radiation induction of the various types of cancer and of how the risks vary with time after exposure.

The understanding of the etiology of cancer is growing rapidly through advances in biology. A notable example is the discovery of oncogenes and their ramifications. A much better understanding of the mechanisms of cancer causation by radiation (among other agents) might be available in a few years, and that might allow much more confident and reliable calculation of radiation risks for low doses under various conditions of exposure and for a variety of host factors. Science recurrently discovers that its appreciation of the details of causation changes as new information becomes available. We are certain that

radiation causes cancer at high doses and high dose rates, but we do not know all the reasons and therefore cannot predict with assurance its carcinogenic potential at low doses and low dose rates.

The four anticipated developments mentioned may require periodic reconsideration of the underlying assumptions, as well as revision of the numeric values in the tables of assigned shares. It is nearly certain that radiation increases the lifetime risk of cancer at some sites and that the size of the increase is related to the size of the radiation dose. Furthermore, the risk may remain increased for a substantial period after a minimal latent interval after first exposure. Whether the increase in risk will remain the same in each successive age bracket as the irradiated persons live their normal life span is not firmly established; at least for the leukemias, it does not seem true. Part of the effect of radiation in inducing cancer could be the bringing forward in time of the development of a cancer that might otherwise have been induced later by other factors. This hypothesis would be plausible if only some individuals in an exposed population were susceptible to the effect of radiation because of genetic factors or exposure to other carcinogens. Thus, age at exposure, time after exposure, age at diagnosis of cancer, and the presence of other risk factors are all relevant to the valid estimation of assigned shares; our understanding of these factors will surely increase as time passes.

c. Changes in Partition

Even if baseline rates were static and risk estimates for radiation-induced cancer had stabilized, a change in the partition might be suggested and would require changes in the tables. Some of the changes might be stimulated by scientific progress in other fields. For example, the interaction of radiation with chemical carcinogens might be clarified, and that knowledge would make it possible to divide the population with respect to exposure to a specific chemical, as the Working Group did for smoking status. Other changes might stem from a social decision that some risk factor should be taken into account or another one ignored in estimating assigned

shares. If Congress or the courts decided that compensation decisions were discriminatory if differentiated by sex, the separate listing of assigned shares for men and women would have to be abandoned, and a joint table constructed. Either type of stimulus would necessitate recalculation of the tables for the new list of risk factors.

3. Consequences of Changes and Uncertainties

A dilemma clearly faces those who must eventually make determinations on the values of assigned share that will justify compensation. These values must be placed, as far as possible, at the most appropriate point whereby risk is fairly assessed. Consistent underestimation of risk is against the interests of the claimants who were truly harmed by radiation. Consistent overestimation of risk is against the interests of the rest of the population, who will in one way or another pay for the excessive awards. Although the calculation of assigned shares may be unbiased at any specific time, new knowledge may easily change the outcome of a claim that was based on an earlier state of knowledge. Under S. 921, a person whose claim was resolved under one set of tables could request a new determination of compensation if the tables changed in his or her favor, but apparently would not be affected by a change in the opposite direction. The Oversight Committee agrees that it might be infeasible as well as impolitic to recover from the latter class of awardees; an alternative approach would be to stipulate that no reconsideration is possible after a claim has been settled. Still other options are readily conceived. The choice between these paths might be illuminated by studying the sensitivity of projected total compensation amounts to the uncertainties in the assigned-share calculations. If the potential differences in compensation seem too great, given the degree of uncertainty, it may be prudent to delay implementation of the tables as a compensation tool until the science base has been improved. But such a decision would also require a similar analysis of the potential errors of the tort-claim system under its present and projected future modes of operation.

The Oversight Committee recognizes that uncertainty is the rule in the application of science to social problems and that the current radioepidemiologic tables could provide important information. The issue may therefore be, not uncertainty itself, but the potential for the uncertainty to be reduced. Within a few years, the uncertainties in the assigned shares might be substantially reduced by a reassessment of radiation and cancer in the Hiroshima and Nagasaki populations through revised dosimetry, data from an additional 4, 8, or even 12 years on cancer incidence and mortality, and improved methods of analysis. As a result, many of the estimates in the tables could soon change markedly and seriously affect the amount of compensation that might be awarded a claimant. Such changes would cause confusion and might damage the credibility of the assigned-share concept.

> The Oversight Committee believes that release of the current radioepidemiologic tables should be accompanied by explicit comment on their limitations.
>
> Furthermore, the Committee believes that a delay in mandating their application should be considered, until such uncertainties are substantially reduced by use of new data and methods.

If Congress decides not to delay implementation of the tables, then it would be important to have a clear plan for adjusting the treatment of compensation cases that were decided before the first major revision of the tables, such as that proposed in S. 921.

The Oversight Committee agrees with the Working Group that a standing committee would be best suited to revise the tables of assigned shares. With sufficient monetary and personnel resources and sufficient time to conduct original analyses, the standing committee could carry out many of the Oversight Committee's recommendations. The standing committee could help to ensure that the automatic revision

system is implemented, that changes in scientific knowledge are continually monitored for relevance to the tables, that new techniques are used when they become available, and that the tables are revised in a timely fashion when that is justified, rather than at predetermined intervals. Otherwise, the need for revision may be forgotten, the revisions may be delayed too long, or a new ad hoc group constituted to revise the tables may find itself with insufficient time to perform its task.

B. Applicability of Tables

The Orphan Drug Act mandates that radioepidemiologic tables be prepared, but does not mention uses contemplated for them. S. 921 provides that the tables would be used as the basis for settling claims against the federal government by citizens exposed to fallout from nuclear weapons tests, by uranium miners employed in federal mines, and by service personnel exposed to radiation at nuclear weapons tests. It does not mention use of the tables for claims against private parties, such as physicians who use diagnostic or therapeutic radiation. Judicial or administrative interpretations could easily broaden the use of the tables. In fact, S. 921 may encourage claims for injuries from other sources of radiation through wording that seems to permit claims to be made separately for such radiation, presumably through the established tort-claims system.

The Oversight Committee notes that tables created for the specified types of claims against the government may not apply, in a scientific sense, to other types of claims. The current tables are designed to apply to a claimant drawn from the general population, whereas a person who is irradiated medically is different from a random member of the general population, because of the medical circumstances that led to his or her irradiation. The clearest example is the development of a second primary cancer in a person who received radiotherapy for a first cancer (see Appendix H). Such differences may mean that an assigned share calculated for a person of the same sex, age at exposure, and age

at diagnosis and with the same dose may not be appropriate for the person who received medical radiation.

Other differences between the uses specified in S. 921 and broader ones include whether the irradiation was intended to be beneficial (as in medical radiation) and whether it was within accepted standards for radiation protection (e.g., for occupational exposures). For these reasons, Congress may wish to be specific about the applicability of the tables of assigned shares to classes of people other than those specified in S. 921.

The concept of assigned shares could be extended to "toxic torts" (cases involving exposures to chemicals, especially carcinogens), although the radioepidemiologic tables would have no relevance there. If the assigned-share concept were used for compensation decisions involving carcinogens other than radiation and if some of the carcinogens interacted with radiation in other than an additive, mutually exclusive fashion, problems could arise from multiple claims by the same person.[21] Congress may wish to consider how to deal with such possibilities.

C. Implications for Existing Radiation Protection Standards

The Radiogenic Cancer Compensation Act (S. 921) does not propose that the assigned-share concept be applied to persons who claim that their cancers resulted from civilian occupational exposures to radiation. However, attempts will probably be made to extend the concept to such claims--to equate the concept to established workman's-compensation systems. Those attempts may have unexpected consequences for standards of protection for occupational exposure to radiation or for standards of radiation protection for the general public.

Two distinct issues are related to the tables' possible impact on standards. One entails the consistency between the information used to develop standards and that used to estimate assigned shares. The other

involves the perception of the effectiveness of standards when nonzero assigned shares can be calculated.

Standards for radiation protection and calculations of assigned shares both begin with appraisals of the risks of radiation. Cancer risks play an important role in deciding on acceptable exposures to radiation in the workplace. Inasmuch as the tables of assigned shares and the radiation protection standards are and probably will continue to be developed by different organizations, different interpretations of the same scientific data base might emerge, and the cancer risk estimates for specific exposure situations might differ. Such differences might cause problems. The Oversight Committee suggests that consistency in approaches to risk estimation between the organization responsible for the tables and the various organizations responsible for standards is desirable and should be encouraged.

International and national radiation protection guides since 1957 have promulgated a maximal permissible radiation dose of 5 rems/year (0.05 Sv/year) to persons occupationally exposed to radiation.[45] However, this guidance was not intended to imply that no risk at all would occur from working at any point below the annual limit for an occupational lifetime of, say, 20 years. Thus, a small fraction of the cancers that eventually occur in radiation workers may be related to their occupational exposures to radiation.

The Oversight Committee notes that there is no necessary contradiction in compensating cases for which established standards were not exceeded, because standards are intended to reduce risk, but cannot eliminate all risk.[32] Some assigned shares would exceed 10%, but there would not be very many such cases. The number could be estimated by considering the distribution of doses over time known to occur in these workers, the expected number of excess cancers by type from these doses, and the number of baseline cancers expected.

The Oversight Committee suggests that, when the radioepidemiologic tables are released, the federal government may wish to issue a statement that indicates whether the assigned-share concept was intended to apply in workplaces other than government-operated uranium mines and discusses the government's position on any perceived inconsistency between the tables and existing standards.

D. Compensation Formulas and Systems

Assuming that Congress will specify precisely what groups of people may be eligible to use the tables in compensation claims, an important question is the relationship of the assigned-share value to the amount of compensation to be awarded. Tort law is presumed to decide in favor of the plaintiff if the preponderance of the evidence favors the plaintiff. This finding is essentially equivalent to calculating an assigned share greater than 50%. Thus, the corresponding compensation formula would award full compensation if the assigned share were greater than 50%, and no compensation if it were 50% or less (Figure VII-1a).

In any compensation scheme, the determination of the maximal award for proven cause should depend on the cost of medical care, the loss of earning capacity, and the value, if any, placed on pain and suffering or on the years of life lost or expected to be lost. For many easily recognized occupational injuries and diseases, compensation is based on relatively well agreed-on methods for compensation.[4]

S. 921 proposes to make the determination of an assigned share explicit through the use of the radioepidemiologic tables and to award compensation for some values of assigned share less than 50%, in particular for values between 10% and 50%. In that region, an award would be limited to an amount equal to the product of the value of the assigned share and the monetary amount appropriate if causation were proved. If the maximal award were set at $500,000 in consideration of

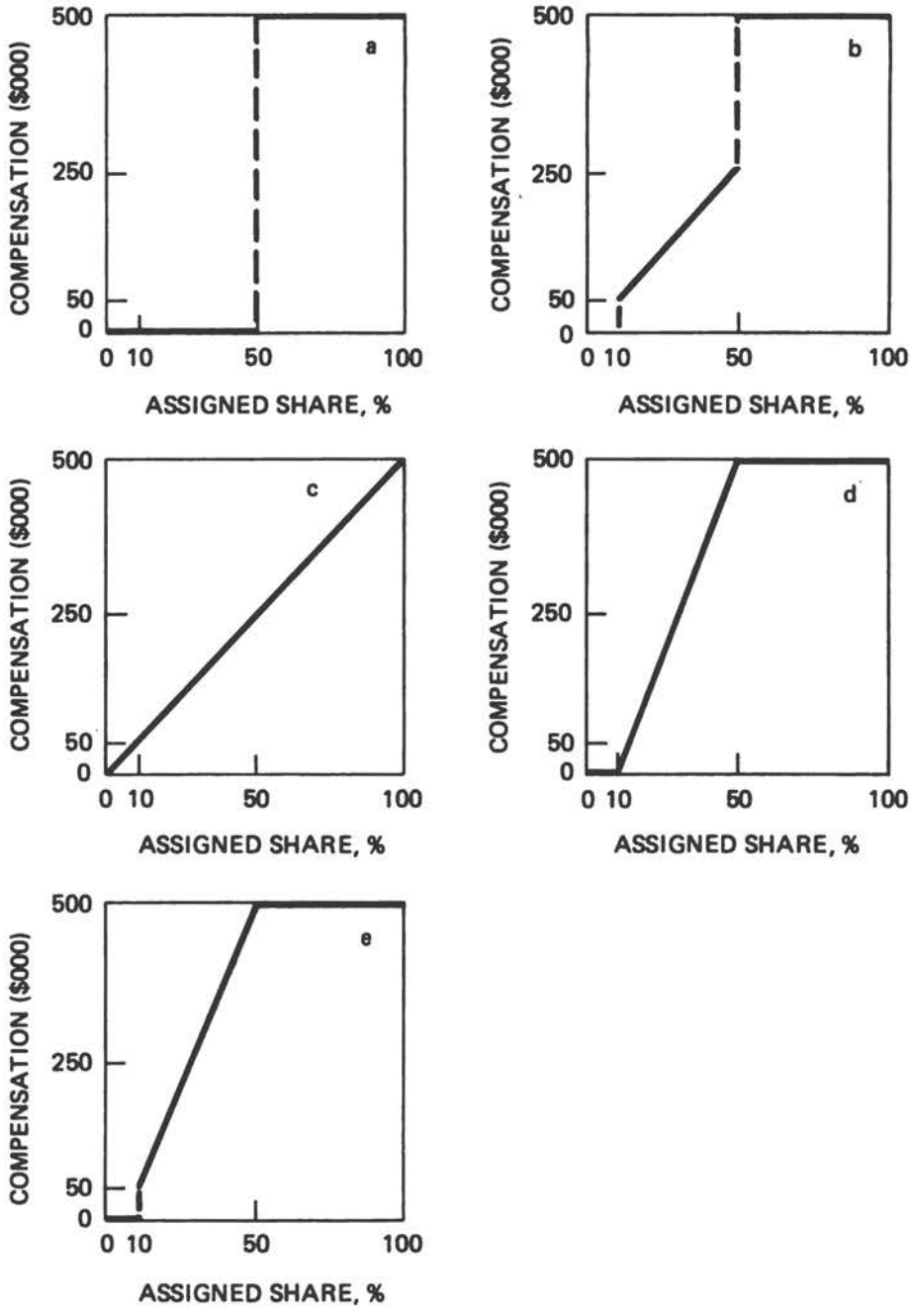

FIGURE VII-1 Selected possible compensation rules based on assigned shares. In each case, the maximal compensation for proven cause is assumed to be $500,000. Actual awards could fall anywhere under the curves, depending on the type of cancer and other factors. a, implied tort-law rule. b, S. 921 rule. c, proportional rule. d, e, hybrid rules. Dashed vertical lines show discontinuities.

the type of cancer and characteristics of the claimant, a claimant with a 40% assigned share could be awarded 0.4 x $500,000 = $200,000 (Figure VII-2b).

For assigned shares greater than 50%, claimants would remain eligible for 100% of the maximal amount under S. 921. The authors of S. 921 may have felt that assigned shares over 50% should earn the same compensation as under tort law. They may also have felt that a lower cutoff value was needed to discourage trivial claims and set it at 10%, below which no awards would be made.

Relative to the tort-law rule, the total compensation of all claimants might increase with the formula proposed in S. 921. The awards to be made between 10 and 50% would be in addition to those made over 50%, which theoretically should be the same as under the tort-law model. A proportional-compensation rule (Figure VII-1c) would tend to even out the losses and gains relative to the tort system, depending on the number of claimants with various assigned shares, but would introduce two problems. First, it would give less compensation to claims falling between 50% and 99%, which would have received full compensation under tort law. Second, it could generate a plethora of small claims whose administrative cost could be high.

In contrast, the total compensation might decrease if court decisions currently result in full awards for situations that would yield assigned shares considerably less than 50%. Already, decisions have been made in favor of plaintiffs who would have been assigned shares by the Working Group's method considerably less than 10%. Such decisions may have in effect determined whether it was more likely than not that the radiation <u>contributed</u> to the cancer (see, for example, the decision by Jenkins[34]).

The proposed lower limit of 10% may pose a problem, because it does not appear to have any coherent scientific or intuitive basis. The proportional rule eliminates the arbitrariness. One hybrid rule

(Figure VII-1d) preserves the 10% cutoff, but eliminates the discontinuities at 10% and at 50%. Under S. 921, a 49% assigned share could earn a 49% award, whereas a 51% assigned share could earn 100%, and intense legal maneuvering would probably follow. A similar problem occurs near 10%. Figure VII-1e presents another hybrid rule that eliminates the discontinuity at 50%, but allows a 10% assigned share to earn a 10% award.

Congress may decide that discontinuities in a compensation formula form an acceptable social policy. If it does, it may wish to take account of the substantial degree of uncertainty in the estimation of the assigned shares. In many cases, the compensation awarded may be markedly different for assigned shares well within the uncertainty limits of the calculation. The same may be true, of course, for tort law. Congress may wish to consider other compensation formulas in the framework of assigned shares before mandating any compensation scheme.

Congress may also wish to reevaluate the relative merits of judicial versus administrative processing of radiation-related cancer compensation claims. The issues have been delineated by Schwarz[59] in Congressional testimony; he cautioned against the mixing of administrative and tort-law compensation systems.

Once tables of assigned shares are created, information on the number of exposed cancer victims, the distribution of their doses, and the proposed compensation rules can be combined to attempt to estimate the total compensation likely to be awarded. Congress may wish to evaluate the long-term costs and consequences of the proposed compensation system in comparison with those of the tort-law system, attempting to anticipate unexpected claims and unexpected behavior of the courts or administrative tribunals.

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APPENDIX A

THE MATHEMATICS OF ASSIGNED SHARE

Consider a nonexposed population that is homogeneous with respect to gender, race, and any other factors that affect the risk of some specific type of cancer. The baseline age-specific cancer incidence rate, denoted h(t:0), is defined as the probability of developing (to the point of diagnosis) this type of cancer at age t, provided that it had not developed before age t. Thus, for example, if 75 of 100,000 men aged 55 develop lung cancer between their fifty-fifth and fifty-sixth birthdays, then h(55:0) = 75/100,000. Let h(t:d) denote the cancer incidence rate for the same population if all men had been exposed to d rads of radiation at age t_0, where $t_0 < t$. Then, among N exposed men of age t, Nh(t:d) cancers would be expected, so the number of excess cancers "due to" radiation is Nh(t:d) - Nh(t:0). The proportion of all cases of the specified type of cancer "attributable" to radiation is thus

$$\frac{Nh(t:d) - Nh(t:0)}{Nh(t:d)} = \frac{h(t:d) - h(t:0)}{h(t:d)} .$$

Hence, the a posteriori chance that any one of the cancer cases was "due to" radiation is

$$AS(t:d) = \frac{h(t:d) - h(t:0)}{h(t:d)} . \qquad (A\text{-}1)$$

We assume here that h(t:d) is not less than h(t:0). If it is, we must decide whether to allow negative assigned shares or to set AS(t:d) to zero. Note that the assigned share depends on age (t) and dose (d). It also depends on age at exposure (t_0), because susceptibilities may differ and affect h(t:d), although that is not explicit in the notation.

The notion of assigned share can also be derived from a "competing-risks" model. Suppose a person is subject to a risk of cancer from a

specified exposure to radiation (r_1), to a risk of cancer from other causes (r_2), and to a risk of death (r_3). We imagine that the risks compete with one another, and we let T denote the earliest age at which one of those events occurs. Let the indicator variable b denote whether the first event is r_1 (b = 1), r_2 (b = 2), or r_3 (b = 3). If cancer is diagnosed in the person at age t, the chance that it is due to radiation, AS(t:d), is:

$$AS(t:d) \stackrel{def}{=} Prob(b = 1:T = t, b = 1 \text{ or } 2). \qquad (A\text{-}2)$$

Now suppose that $h_1(t)$, $h_2(t)$, and $h_3(t)$ denote the cause-specific hazard rates corresponding to r_1, r_2, and r_3, respectively. That is,

$$h_j(t) = \lim_{t \to 0} [Prob(t \leq T < t + \Delta t, b = j:T \geq t)/\Delta t] \qquad (A\text{-}3)$$

for j = 1, 2, 3. In words, $h_j(t)$ is the conditional probability that the person succumbs to risk j at age t, given that the person has not succumbed to any risk before age t. Given these functions, it follows from Equation A-2 that

$$AS(t:d) = \frac{h_1(t)}{h_1(t) + h_2(t)} . \qquad (A\text{-}4)$$

However, $h_1(t) + h_2(t) = h(t:d)$, the combined cancer incidence rate for exposed persons, and $h_2(t) = h(t:0)$, the cancer incidence rate for nonexposed persons. Thus, $h_1(t)/[(h_1(t) + h_2(t)]$ reduces to Equation A-1, the population-based definition of assigned share.

The competing-risks rationale of assigned share has the disadvantage of introducing the notion that two separate competing cancer risks operate within a given person. This notion would be objectionable to some. The population-based definition of assigned share circumvents this type of problem by interpreting probabilities on a population level, rather than on an individual level, and therefore

may be more acceptable. Furthermore, the population-based definition of assigned share still applies if synergism is in effect, in that one can speak of the numbers of persons who develop cancer in exposed and nonexposed populations.

$$AS^*(t:d) = \theta Hd/(H^* + \theta Hd) \qquad (B\text{-}5)$$

$$= \theta d/(H^*/H + \theta d).$$

Thus, by comparing Equations B-2 and B-5, it can be seen that a U.S. AS will be larger than the corresponding Japanese AS whenever H*/H is less than 1 and smaller whenever H*/H exceeds 1. For example, because U.S. breast-cancer incidence is much larger than that in Japan, H*/H will be large, so the U.S. AS* (Equation B-5) will be smaller than the Japanese AS (Equation B-2). Table B-1 illustrates this point.

TABLE B-1

Variation in Assigned Share with Ratio of Baseline Risks in Japan (H) and the United States (H*) for Selected Relative Risks (RR) in Japan

			Values of AS*(t:d) for Various H*/H				
Relative Risk (Japan)	d[a]	AS(t:d)	0.25	0.5	1	2	4
1.2	0.2	0.17	0.44	0.29	0.17	0.09	0.05
1.5	0.5	0.33	0.67	0.43	0.33	0.20	0.11
2	1	0.50	0.80	0.67	0.50	0.33	0.20
5	4	0.80	0.94	0.89	0.80	0.67	0.50

[a] In multiples of doubling dose.

For example, suppose that--for a specific cancer, dose, and age at exposure--the relative risk in Japan is 1.2, so that the Japanese AS is 0.17. Then, if the cumulative incidence ratio is H*/H = 0.25 (i.e., 4 times higher in Japan), the corresponding U.S. AS is inflated to 0.44. If the cumulative incidence in the United States is twice that in Japan, then the U.S. AS is shrunk from 0.17 to 0.09. For breast cancer, H*/H can be large--say, 4 or more--so a U.S. AS can be markedly smaller than the Japanese value. The opposite holds for stomach cancer, of which the Japanese incidence is much larger than the U.S. incidence.

Unfortunately, few data are available to check the accuracy of the projection assumption (i.e., Equation B-4). The assumption was empirically motivated by comparing Japanese atomic-bomb data with U.S. mastitis and fluoroscopy data. However, there are no comparable U.S. data on any other cancers, and therefore no empirical bases for assessing the validity of the assumption.

A technical point worth noting is that, in general, the ratio

$$H^*/H = \frac{\int_{t_1}^{t_2} h^*(t)dt}{\int_{t_1}^{t_2} h(t)dt} \qquad \text{(B-6)}$$

depends on the specific ages, t_1 and t_2, used to evaluate the cumulative incidences. Thus, use of t_1 = 25 years and t_2 = 40 years will lead to degrees of shrinkage or inflation of a Japanese AS <u>different</u> from use of t_1 = 25 years and t_2 = 50 years. To get an idea of how much an AS can be affected by the choice of t_1 and t_2, the Committee used the data on Japanese and U.S. breast-cancer incidence depicted in Figure 2 of Land <u>et al.</u>[1] From those curves, the Committee estimated H^*/H = 2, 3, or 4 for (t_1, t_2) = (25, 40), (25, 50), and (25, 60), respectively. Thus, the cumulative incidence ratio is about 2 for the period 25 to 40 years and about twice that for the period 25 to 60 years. The choice of followup time can have a marked effect on AS*. For example, a Japanese AS of 0.50 would be projected to a U.S. AS of 0.33 if the Japanese data were followed to age 40, but to 0.20 if they were followed to age 60. It seems that no projection method ought to have such a property. The shrinkage or inflation of a Japanese AS will depend on the choice of t_1 and t_2, unless the baseline U.S. and Japanese incidence rates are proportional, i.e.,

$$h^*(t) = \delta\, h(t), \qquad \text{(B-7)}$$

for some constant δ.

When the two baseline rates are proportional, the projection model (Equation B-5) can be written

$$AS^*(t:d) = \theta d/(\delta + \theta d). \qquad \text{(B-8)}$$

In practice, θ will be estimated by comparing nonexposed and exposed Japanese populations, and δ will be estimated by comparing baseline U.S. and baseline Japanese populations. That would be simpler and statistically more efficient than the method currently used. However, it is not clear what would be appropriate if the assumption in Equation B-7 did not hold.

The projection model (Equation B-5) has a physical interpretation. Note that $H(t:d) - H(t)$ is the area between the incidence functions $h(t:d)$ and $h(t)$ from ages t_1 to t_2; i.e.,

$$H(t:d) - H(t) = \int_{t_1}^{t_2} [h(t:d) - h(t)]dt. \qquad \text{(B-9)}$$

The difference can be thought of as the excess cumulative Japanese incidence for the interval (t_1, t_2).

The projected U.S. risk for an exposed person is described by the incidence function $h^*(t:d)$ and is taken to be the function for which

$h^*(t:d)$ is proportional to $h^*(t)$, the baseline U.S. incidence

and

$$H^*(t:d) - H^*(t) = H(t:d) - H(t).$$

Thus, the excess Japanese cumulative incidence is "spread" over $h^*(t)$ to determine $h^*(t:d)$, and the latter is used to estimate the U.S. AS.

Because the procedure described above depends on the proportionality of the Japanese and U.S. baseline incidence rates over age, the Working Group should provide evidence to support that proportionality or consider a different method for transferring risk estimates from Japan to the United States.

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APPENDIX C

ANALYSIS OF LEUKEMIA DATA FROM JAPAN

Section IV D discusses several possible methods of estimating assigned shares. Essentially, we need to estimate the hazard function for a specified kind of cancer for a person who was exposed to radiation dose d and for a similar person who was not exposed. The purpose of this appendix is to give further details of the method illustrated by Brodsky et al.[2]

The sample used by Brodsky et al. consisted of the atomic-bomb survivors in Japan, and the cancer was leukemia. For every person in the sample who was alive and without cancer at the start of time interval t, we observe gamma kerma G, neutron kerma N, age t_0 at exposure, and sex s, none of which depends on t. We can construct a large matrix of the observations, in which each row corresponds to a different person and one column corresponds to each specified characteristic. We need one additional column to describe the state of each person with respect to the diagnosis of cancer during time interval t. A 1 or a 0 is entered according to whether cancer was or was not diagnosed. Note that we are interested in estimating incidence probabilities, so we want the first diagnosis of cancer. However, Brodsky et al. were concerned with mortality estimates, so the event of interest to them was death from leukemia during interval t.

We want to study the effect of kerma G and of kerma N for successive periods since exposure. As stated in Section IV D, we anticipate that the effect will be small for some time after exposure, because the cancer will not have developed enough to be detected and diagnosed. The effect may then increase and later decrease when all cancers have been detected. Data are available for 1950-1978. The method used was to split the 28-year period, preliminarily, into four equal intervals (or to split it into eight intervals or to consider it as a single interval). The preliminary study looked for time effects

in the coefficients appearing in the model; Brodsky et al. looked at the additive model (Equation IV-2). The procedure was to estimate coefficients a, b_1, b_2, c, d_1, d_2, and d_3 for each interval separately. This was done with a statistical package program, such as GLIM,[1] which can produce a set of estimates by using maximum likelihood estimation, minimum chi-square (minimum deviance), or least squares. The variability can be specified as a normal deviation from the expected, or it can be multinomial or Poisson. Clearly, each interval should be examined with the same set of procedures, and each interval studied separately from the others. Because each interval is short, the precision of the estimators cannot be very good, but we now are looking for evidence of a trend as the years go by. This suggests looking at the coefficients obtained, side by side, for the four intervals (and then for the eight intervals and for the entire 28 years).

Brodsky et al. found that interaction effects d_2 and d_3 were essentially zero and dropped them. Because the nonexposed persons were selected for the sample by matching their characteristics with those of the persons with high kerma, that result is not surprising. Indeed, with this system of sampling, it is almost impossible to find an interaction effect even if it exists. They also noted that some of the models (e.g., linear or linear-quadratic in gamma-ray kerma) fitted slightly better than others, but the value of the test criterion differed little; it was a mortality study. They plotted the most interesting coefficients--kerma effects b_1, b_2, and c--with error bars of one standard deviation, as in Figures C-1 through C-4. On each plot are the four estimates obtained when the 28 years are divided into four parts, the eight estimates when the division is into eight parts, and the one estimate when all 28 years are used. Each estimate is plotted at the middle of the interval (expressed in months) to which it corresponds. The estimated coefficients change rather smoothly with time since 1950 (5 years after the exposure), and a simple interpolation curve was fitted to each changing coefficient. Both b_1

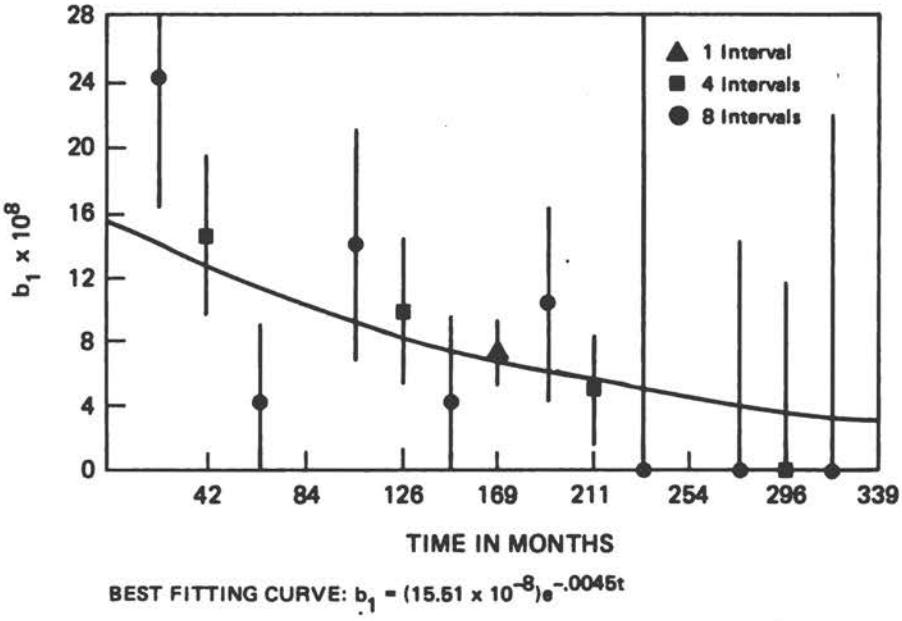

FIGURE C-1 Regression estimates of b_1 for L-L model. Reprinted with permission from Brodsky *et al.*[2]

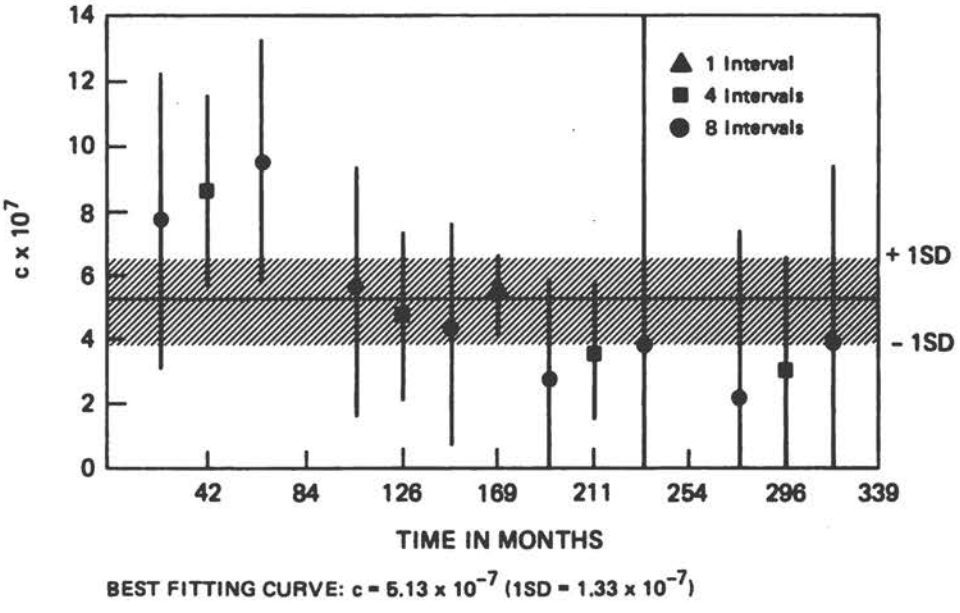

FIGURE C-2 Regression estimates of c for L-L model. Reprinted with permission from Brodsky *et al.*[2]

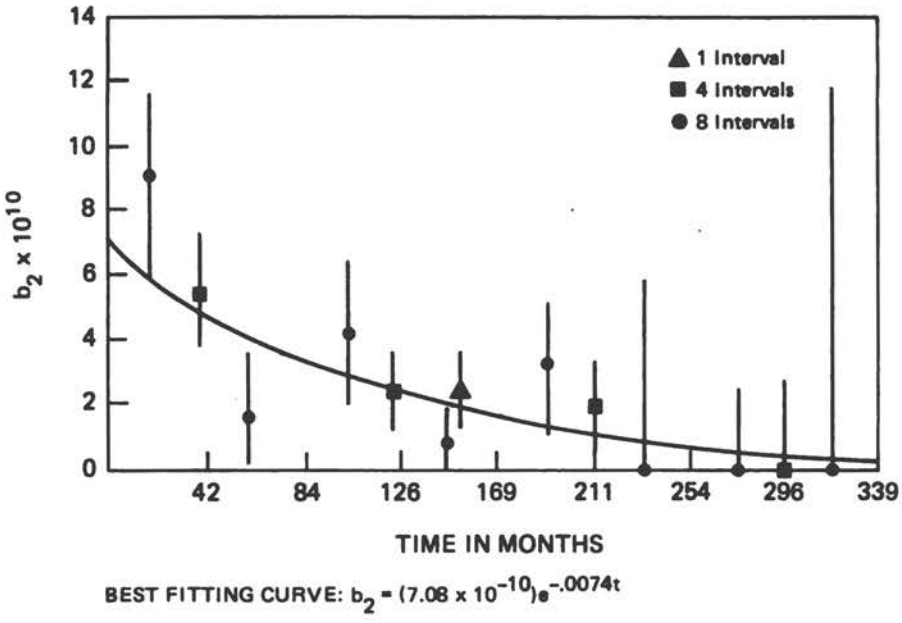

FIGURE C-3 Regression estimates of b_2 for Q-L model. Reprinted with permission from Brodsky et al.[2]

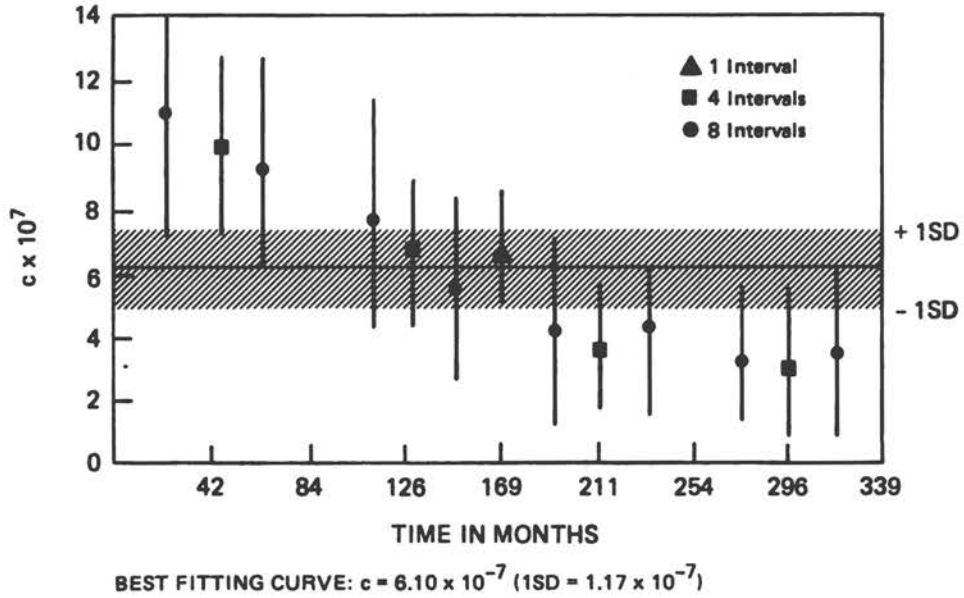

FIGURE C-4 Regression estimates of c for Q-L model. Reprinted with permission from Brodsky et al.[2]

b_2, the linear and the quadratic coefficients for gamma radiation, are decreasing. So is c, the effect of neutron radiation, in the case of the model that is quadratic in gamma-ray kerma (Figure C-4).

Once the smoothly changing interpolation curves expressing time dependence are approximated, they can be combined with the additive model (Equation IV-2)--and a corresponding preliminary analysis could have been done for the multiplicative or the logistic model--to produce the final model. In this way, the time-dependent additive model was constructed.

The hazard functions will be changing smoothly with total kerma d, with age at exposure t_0, and with age at death t. One would expect similar hazard functions for biologically similar cancers, or at least for cancers that are not very different. It may be possible to use this smoothness with changing kind of cancer to improve the estimates of the hazard functions for rare cancers. Given the smoothly changing hazard functions, it is easy to compute tables of assigned shares, which will also be changing smoothly. No further smoothing is needed or desired.

As discussed in Chapter V, mortality data may be more reliable than incidence data. We therefore expect the tables of assigned shares for death from some cancers to be more precise than the corresponding tables for incidence. Clearly, two such tables do not answer the same question, but they should support each other. This comparison is not the same as trying to convert a mortality rate into an incidence rate, which provides very uncertain estimates. It may be desirable to compute separately the two tables of assigned shares, each of which is of interest, and to regard one as partial support of the other.

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APPENDIX D

STUDIES OF THE RELATIONSHIP BETWEEN RADIATION AND MORTALITY FROM MALIGNANT NEOPLASMS AMONG ATOMIC-BOMB SURVIVORS

An analysis of cancer mortality data from the Japanese atomic bomb survivors was attempted to study the sensitivity of risk estimates to different models and to determine whether a smooth analytic technique would give different answers than the stratified analysis employed by the Working Group. In summary, these analyses of the dose-response relationship indicated the following:

1. The age at time of exposure and the age at time of death both have large effects on mortality, positive and significant. Their interaction tends to be negative and is also significant. This means simply that younger persons tend to die at longer times after exposure.

2. For those cancer sites where it can be studied, the effect of sex also is important, with women showing lower risks of death than men.

3. In the presence of other strong effects, the effects of radiation are less well determined. For the types of cancer studied here, the quadratic term in a linear-quadratic fit to the data tends to have a negative coefficient, but it is not significant (and thus can be excluded from consideration). The neutron kerma term is also not significant.

4. In general, a model with a positive coefficient for the quadratic term in gamma kerma will not fit the observations, especially if there is also a linear term.

5. The power of the tests (the ability to detect an effect if it exists) is high in those cases testing whether we can exclude an effect of age at time of exposure, an effect of age at time of death, an effect of sex, or any combination of these effects. Unfortunately, the

power is small, often very small, with these data whenever we try to test something about the effect of radiation. We conclude that the atomic bomb survivor data set (as of 1978) is not large enough to distinguish between the various possible dose-response models.

6. Thus, we are not able to come to a definite choice of dose-response model so far as radiation is concerned. The risks predicted by the various models are different, and the differences depend on the values of the other variables in a complicated way.

7. The dependence on the other variables, such as age at exposure, is different from the dependence adopted by the Working Group, and so are the predicted risks, especially for stomach cancer.

8. The data available to us extend only through 1978. Additional cancer deaths will occur, especially in the age groups that were young at the time of exposure. Also, all radiation estimates are under revision. Therefore our results are tentative.

The studies summarized above originated with efforts to get better information on the dose-response relationship at low doses. Extensive data are required for reliable estimation of the relationship. The atomic-bomb survivors provide a very large group of people who received rather large doses and even more who received smaller doses. Although not constituting a random sample, they were selected on the basis that they were in the target area when the bomb fell and survived for 5 years (when data collection started). Other data sets are much smaller and tend to involve people who had specified diseases that were treated with radiation or who were associated with particular occupations, economic statuses, or other factors known to affect cancer mortality.

We can study the cancer experience of the population of atomic-bomb survivors as a function of the radiation received, taking into account differences in age at the time of bombing (ATB), age at the time of diagnosis or death (ATD), number of years between exposure and time of

death, and sex. The period between exposure and diagnosis is confounded with ATB and ATD, because all persons received their exposure in the same year (1945). We can also study selected interactions between the variables, all for each organ separately. We hope to find with this analysis more reliable relationships between exposure and the probabilities of having cancer diagnosed or of dying from cancer.

The data available to us are in the tables of deaths from malignant neoplasms among atomic-bomb survivors from 1950 to 1978.[3] Because the Orphan Drug Act mandates that the tables be based on incidence, we would like to have tumor-registry data. Such data from about 1959 exist, but they do not seem to be available in Washington, DC, either in print or on tape. For the present, we are using the printed death data.

There are further difficulties with the data. Data on an additional 4 years are ready, but have not been released. The estimates of radiation are undergoing extensive revision. Because these revisions are not yet completed, we have used the published T65 kerma rad estimates that are used in Life Span Study (LSS) Report 9.[3] Although we believe that the relationship between kerma and absorbed doses is sufficiently stable that our analysis can give valuable insight into the nature of the relationship between absorbed dose and cancer mortality, this assumption may prove incorrect when the revised dosimetry is available and the expanded cancer data set has been analyzed.

The published tables provide grouped data with the most detail given for stomach cancer; because many characteristics seem to affect the probabilities of death, it would be desirable to have full information for each kind of cancer. Deaths have been recorded only from 1950 to 1978; persons who were young in 1945 (young ATB) may not be old enough by 1978 to have had a cancer diagnosed or to have died from cancer; the lack of complete ascertainment may confuse our

interpretations. Furthermore, we have no information on persons who died earlier than 1950; this lack of information complicates our analysis of data for people who survived past 1950.

We hoped to find a reliable relationship between kerma and the probability of death. In particular, we wanted to study whether it could be better approximated by a straight line, by a quadratic curve, or by a combination. We also wanted to consider whether more complex relationships are needed--for example, whether the relationship between mortality and kerma depends on sex or ATB, and so forth. Thus, we wanted to allow any sort of response surface for the estimated probability of death, without restrictions. However, although the population studied is large, the available information is still insufficient to discriminate between all possible response surfaces. At the same time, we also wanted to study whether the two types of radiation (gamma and neutron) should be considered separately, because their biologic effects are thought to be quite different in magnitude, or whether they can be combined by some formula into a "total dose." In the latter case, how should the components be weighted, if not by simply adding the two components, as was reported in LSS Report 9?

We have assumed that the probability of getting a specified cancer changes smoothly with kerma and with ATB, age at time of diagnosis, and so forth. Furthermore, there may be interactions among these factors.

We have used direct analysis of the observations, as well as hints from biologic theory, to suggest what models should be studied. We have then added those models that are of special interest in the literature. In consequence, we have examined an array of models. Logistic models form a convenient class of models that fit well for different types of cancers. In this class, the probability of death increases very slowly for low kerma (or for low values of other factors) as a nondecreasing response surface. As any factor becomes more important, the probability increases more rapidly, and then levels off. However, we are considering the probabilities of dying of cancer

in the next year, so they will be small. In fact, they turn out to be in the low part of the response surface and increase essentially linearly with the variable in question. Before selecting specific models to approximate the probabilities, we examine the observed proportions of death from cancer as a function of the parameters in the data.

Many studies consider the dose-response curve without paying specific attention to the characteristics of the individuals. Other studies make comparisons between exposed and nonexposed groups on the basis of total person-years, combining all other characteristics, including duration of exposure. Such groupings may disguise and even confuse the relationships under study. We propose to take as many variables into account as are available and to try to study the effect of increasing radiation in the presence of these other variables. Similar studies have been made for leukemia mortality[1] and for thyroid incidence.[2]

The plots in Figure D-1 show the observed age-specific mortality (average fractions of the population--not number per 100,000--dying from specified types of cancer in a year) as functions of increasing radiation (DOSETOTAL in rads kerma) for several types of cancer (those on which the most complete data have been published). The curves are further separated into several categories of age at exposure (ATB)--where data permit, for the two sexes separately. To make the plots easier to read and to increase the sample sizes in the many subcategories we have considered, we do not divide the data further by the year of death or the age at time of death (ATD), either of which could be used to compute the number of years between exposure and death. There is an increase in the observed mortality as ATB increases, especially for the older groups. Part of the explanation for the lower mortality for the young cohorts is that these cohorts are not yet old enough to have an appreciable baseline death rate from cancers of the types considered--stomach, breast, lung, colon, and "other." This suggests that ATD needs to be considered simultaneously

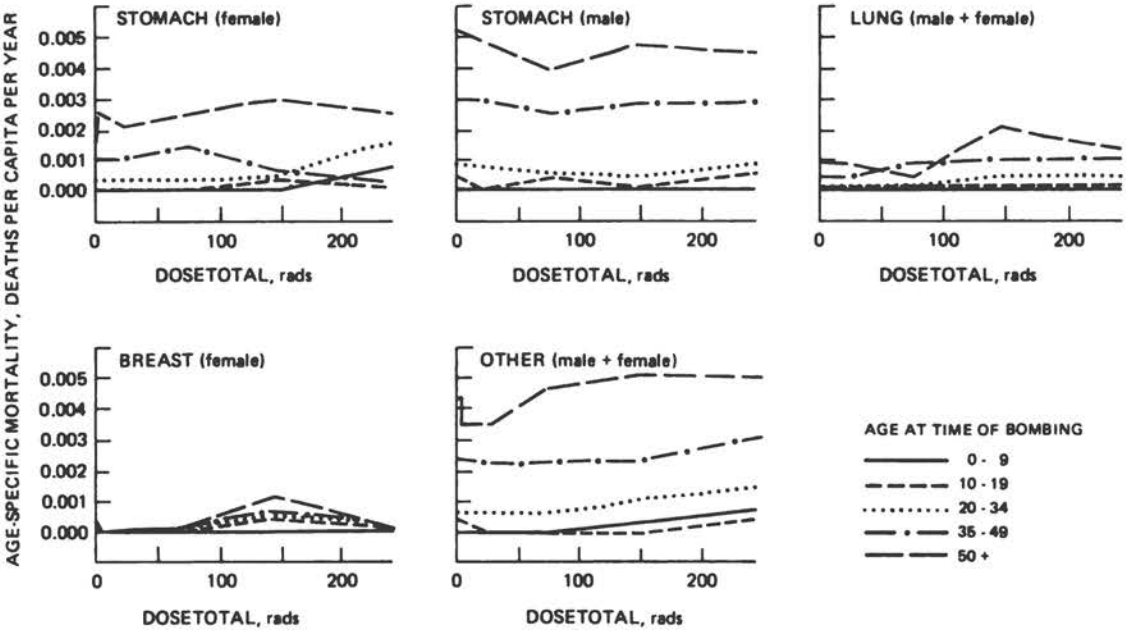

FIGURE D-1 Observed age-specific mortality versus DOSETOTAL for various ATB by sex and site of cancer.

with ATB. In Figure D-2, the plots show the mortality corresponding to different ATD for several types of cancer and sex, when available. The categories of ATB have been combined. An effect of ATD is apparent, corresponding to increasing mortality with increasing age. Part of the observed effect of ATD may actually be due to the effect of year of death or of years since exposure, owing to confounding. To examine this possibility, Figure D-3 plots mortality versus year of death from stomach cancer. In this representation, there is no large effect--perhaps no effect at all--of year of death. In these plots, the data for various ATB, ATD, and DOSETOTAL have all been combined, although there is evidence that some of these effects may be important. Thus, the plot, although aggregated, does suggest that ATD is more relevant than year of death in explaining the probability of death from cancer.

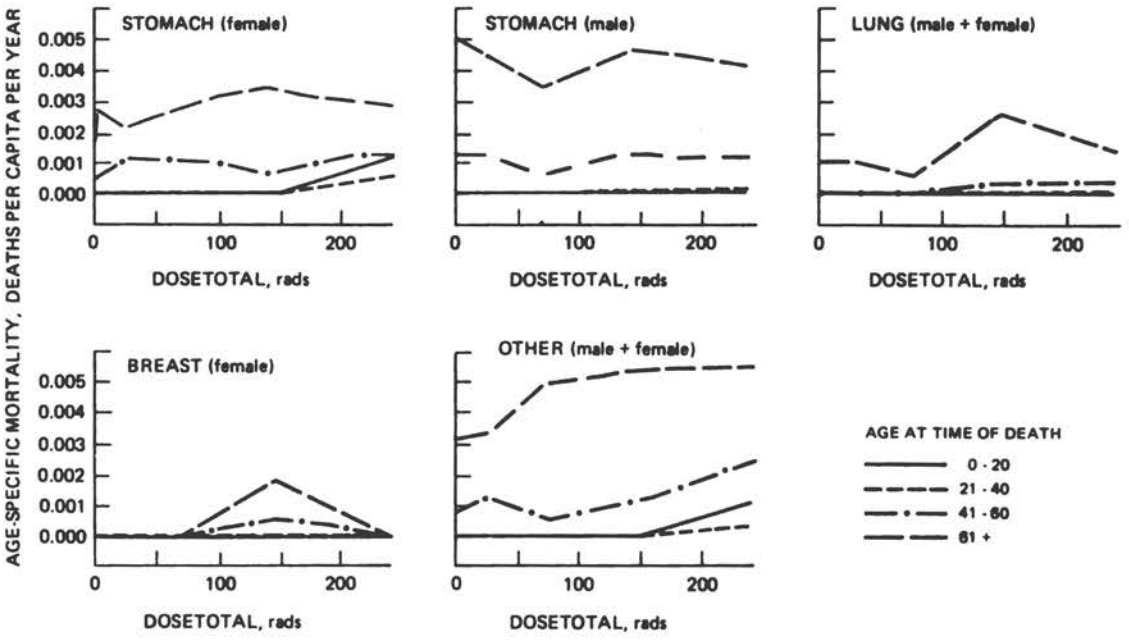

FIGURE D-2 Observed age-specific mortality versus DOSETOTAL for various ATD by sex and site of cancer.

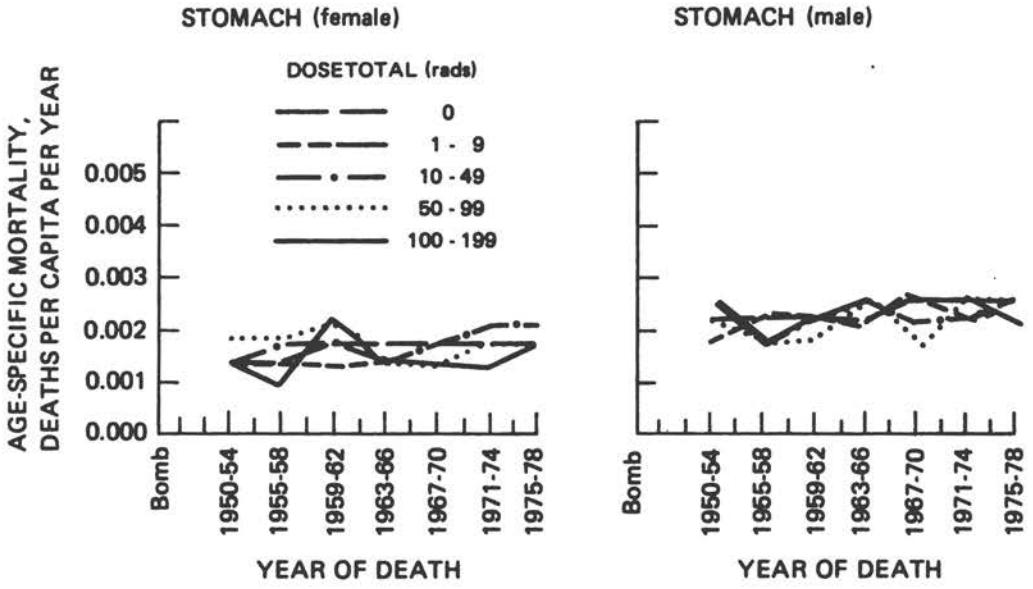

FIGURE D-3 Observed age-specific mortality versus year of death for various DOSETOTAL.

The increases in mortality with increasing ATB or increasing ATD tend to occur with each kind of cancer we have studied. The effect of sex can be studied in detail only for stomach cancer, because the observations have been grouped for the other cancers. Men have much higher probabilities of stomach cancer. A preliminary study of lung cancer, using grouped data, also found higher mortality for men, as expected.

It is of interest to examine these plots as a function of increasing DOSETOTAL. There is little increase for stomach cancer, for colon, or for lung, although some cohorts show some increase followed by a decrease at high dose. This behavior is most pronounced in breast cancer, occurring for every age group. The mortality rates are small, but the changes are very smooth. However, the plots for "other" cancers do show a tendency to increase with kerma for every cohort. The control group, which is published as having zero rads, tends to differ from the group with kerma between 1 and 9 rads;* its mortality is sometimes higher, but more often lower.

The stochastic models we have used take into account the information gained from plotting the observed mortality. We also consider the possibility of both linear and quadratic terms in the gamma kerma, but only a linear term in the neutron kerma. In addition to these kerma terms, the linear effects of ATB and ATD (age at time of death), and the categorical effect of sex, several interaction terms are included. The second-order interactions are DOSETOTAL x ATB, DOSETOTAL x ATD, and ATB x ATD. The third-order interaction term is DOSETOTAL x ATB x ATD. These interaction terms permit complex response surfaces. For example, if the coefficient of DOSETOTAL x ATB is negative, persons who were younger at the time of exposure could develop more cancers for a given DOSETOTAL than those who were older.

* To avoid awkward construction, we do not give equivalents in grays in this appendix.

Death from the kinds of cancer we are studying is very unlikely in young persons, even when they have received substantial radiation. As noted, the plots support this statement. Therefore, we have used ATD (age at time of death), rather than year of death. The kerma categories used are those published, except that most of our studies consider only the six categories below 299 rads kerma, so as to concentrate on the lower levels and to avoid any exposure that may involve appreciable cell-killing effects. Two higher levels were included in special studies of the sensitivity of the coefficients in the models to changes in the range considered. Also, some analyses were made without the zero-kerma group, to see whether this specially selected control group might exhibit patterns different from those of the atomic-bomb survivors. (No strong effect was observed.) Thus, for studies of stomach cancer, the typical number of categories considered is 420. (When all eight categories are used, the total is 560.) The published data give the number of deaths from stomach cancer and the number exposed to risk in each category. The data are not all completely independent, because the same persons are followed through the years and each person can die only once. However, the number of persons in each category is large, especially at the lower levels, and the mortality from stomach cancer in any one year is very small (the plots show that the mortality is smaller than 0.005), so the lack of independence is slight. In this study, we have assumed approximate independence.

We used the method of maximum likelihood (which is equivalent to minimum chi-square for such large samples) to find the best-fitting coefficients for each model. We then tested the goodness of fit of each model. We considered a succession of models, successively eliminating some of the explanatory terms, thus making the model simpler. In each case, we tested whether the term can indeed be excluded without unduly affecting the fit of the model. We first considered models with separate terms for the two kinds of radiation, gamma and neutron. Later, models with only DOSETOTAL were used. We studied the several kinds of kerma terms, then the ATB and the ATD terms, and then the sex term.

The quantity being estimated is the logit of the mortality (more precisely, the logit of the probability of death at a specified age, given the characteristics of the person). The logit is the logarithm of the odds ratio and has the property that, if it is additive, the probability itself must be between zero and unity, first increasing very slowly in terms of the total effects, then increasing more rapidly, and finally leveling off. As noted earlier, the probabilities are so small in these studies that they remain essentially linear in the explanatory variables.

For all the cancers studied, we find that ATB and ATD both have large influences on mortality, with coefficients that are positive and significant. That is, they cannot be excluded from the model. Their interaction coefficient is negative and also significant. That means simply that younger persons tend to die longer after the bombing than older persons. In cases in which the data permit us to study the influence of sex, it is also found to be important, with women usually having lower risks than men.

In the presence of these strong effects of ATB, of ATD, and their interaction, the effects of radiation are less well determined. Usually, the quadratic term in gamma kerma has a negative coefficient, but it is not significant and thus can be excluded from consideration. Similar results apply to the neutron kerma coefficient and to the DOSETOTAL coefficient. However, we note that, in all these cases, the standard deviation of the coefficient is about as large as the coefficient itself. Thus, we conclude that we need to examine the power of the test of hypotheses concerning kerma terms. It is of interest that a model that constrains the coefficient of the quadratic kerma term to be positive will generally not fit the observations, especially if there is also a linear term. That result also occurs in leukemia mortality.[1]

A summary of the results is shown in Table D-1. Models 2 through 5 were compared with a model (Model 1) of the form

$$\text{logit mortality} = a_0 + a_1G + a_2G^2 + a_3N + a_4ATB + a_5ATD + a_6S + a_7DOSETOTALxATB + a_8DOSETOTALxATD + a_9ATBxATD + a_{10}DOSETOTALxATBxATD . \quad (D-1)$$

Model 5 forced $a_1 = a_2 = a_3 = 0$, but added terms $a_{11}DOSETOTAL$ and $a_{12}(DOSETOTAL)^2$, where DOSETOTAL = G + N. Models 6 through 8 were compared with Model 5; Model 8 was Model 6 with $a_{10} = 0$; Models 9 through 17 were compared with Model 8. Table D-2 displays the coefficients estimated from the observations for three models for stomach and breast cancer.

Table D-3 shows information about the power of the various tests. The power is high in cases that test whether we can exclude an effect of ATB, ATD, sex, or some combination of them. These are only the cases in which we found that the variables need to be included in the model. Unfortunately, the power is small (often very small) with these data whenever we try to test something about the effect of radiation. The conclusion is that the atomic-bomb survivor data set (as of 1978) is not large enough to distinguish between the various possible radiation effects. It may be that with additional years or more precise and appropriate (i.e., absorbed) doses the power will increase sufficiently, but considerable improvement is needed. The use of incidence data, rather than mortality observations, may help. All the computations shown in Table D-3 refer to DOSETOTAL in the range 0 to 299 rads only, and to a level of significance of 0.05. The power conclusions are not greatly altered by changing these two factors.

Because we are not now able to come to definite conclusions on the choice of model, it is of interest to see whether the mortality predicted by the various models are different. We cannot provide a single answer, because the probabilities depend on ATB, age at death,

TABLE D-1

Significance Probabilities for Comparisons of Successive Models

Model	Hypothesis under Test	Cancer					Can Excl?
		Stomach	Colon	Lung	Breast	"Other"	
2	Exclude gamma-squared (Test $a_2 = 0$)	0.27	1.00	0.32	0.10	0.25	Yes
3	Exclude third-order (Test $a_{10} = 0$)	0.32	0.18	0.65	0.75	0.02	?
4	Exclude neutrons (Test $a_3 = 0$)	1.00	0.58	0.37	0.11	0.75	Yes
5	Use DOSETOTAL (Test $a_1 = a_2 = a_3 = 0$; $a_{11} \neq 0$, $a_{12} \neq 0$)	0.70	0.90	0.90	0.86	0.67	Yes
6	Exclude DOSETOTAL-squared (Test $a_{12} = 0$)	0.48	0.65	0.20	0.03	0.44	?
7	Exclude DOSETOTAL only (Test $a_{11} = 0$; $a_{12} = 0$)	0.24	0.29	0.32	0.12	0.02	?
8	(Models 3 & 6) (Test $a_{10} = a_{12} = 0$; $a_{11} \neq 0$ in this and all models following)	0.47	0.35	0.43	0.08	0.01	No?
9	Exclude second-order (Test $a_7 = a_8 = a_9 = 0$)	0.00	0.00	0.00	0.00	0.00	No!
10	Exclude ATB x ATD (Test $a_9 = 0$)	0.00	0.00	0.00	0.00	0.00	No!
11	Exclude DOSETOTAL x ATB (Test $a_7 = 0$)	0.53	0.07	1.00	0.27	0.01	No?
12	Exclude all ATB (Test $a_4 = a_7 = a_9 = 0$)	0.00	0.00	0.00	0.00	0.00	No!
13	Exclude DOSETOTAL x ATD (Test $a_8 = 0$)	1.00	0.32	1.00	0.53	0.17	Yes
14	Exclude all ATD (Test $a_5 = a_8 = a_9 = 0$)	0.00	0.00	0.00	0.00	0.00	No!
15	Exclude sex (Test $a_6 = 0$)	0.00	0.00	0.00	0.00	0.00	No!
16	Exclude DOSETOTAL interaction (Test $a_7 = a_8 = 0$)	0.29	0.06	0.95	0.45	0.01	No
17	Exclude all DOSETOTAL (Test $a_7 = a_8 = a_{11} = 0$)	0.46	0.05	0.00	0.02	0.00	No!

TABLE D-2

Estimated Values for Coefficients in Logit Models

	Estimated Coefficients under Specified Models[a]					
	Stomach Cancer			Breast Cancer		
Coefficient	Model 1	Model 5	Model 8	Model 1	Model 5	Model 8
a_0	-13.3	-13.3	-13.2	-13.4	-13.4	-13.2
a_1	-0.012	--	--	0.059	--	--
a_2	0.20 E-4	--	--	-0.226	--	--
a_3	0.122	--	--	-0.92 E-4	--	--
a_4	0.084	0.084	0.081	0.078	0.078	0.071
a_5	0.115	0.115	0.114	0.076	0.076	0.074
a_6	-0.759	-0.759	-0.758[b]	--	--	--
a_7	-0.17 E-3	-0.17 E-3	-0.45 E-4	-0.46 E-3	-0.46 E-3	-0.22 E-3
a_8	-0.94 E-4	-0.95 E-4	0.13 E-4	0.76 E-4	0.79 E-4	0.12 E-3
a_9	-0.13 E-2	-0.13 E-2	-0.12 E-2	-0.12 E-2	-0.12 E-2	-0.12 E-2
a_{10}	0.20 E-5	0.20 E-5	0.0	0.28 E-5	0.28 E-5	0.0
a_{11}	0.0	0.0067	0.0031	0.0	0.0204	0.0053
a_{12}	0.0	0.54 E-5	0.0	0.0	-0.53 E-4	0.0

[a] E-4 means times 10^{-4}, and so on. Coefficients that are not well determined (a_1, a_2, a_3, a_7, a_8, a_{10}, a_{11}, and a_{12}) are all concerned with kerma and are unstable when organ is changed. Coefficients for stomach cancer yield results very different from those of method used by Working Group.

[b] Male = 0; female = 1.

TABLE D-3

Summary of Power[a] of Tests of Various Models

Nature of Test	Cancer				Power is
	Stomach	Lung	Breast	"Other"	
Test Model 2 against Model 1 (Can we exclude gamma-squared?)	0.20	0.18	0.38	0.20	Poor
Test Model 3 against Model 2 (Can we exclude third-order?)	0.20	<0.10	<0.10	0.63	Poorer
Test Model 4 against Model 3 (Can we exclude neutron kerma?)	<<0.10	0.11	0.33	0.10	Poorest
Test Model 6 against Model 5 (Can we exclude $DOSETOTAL^2$)	0.10	0.21	0.60	0.10	Poorer
Test Model 7 against Model 5 (Can we exclude DOSETOTAL?)	0.20	0.18	0.31	0.62	Poor
Test Model 8 against Model 5 (Can we exclude $DOSETOTAL^2$ and third-order?)	0.21	0.23	0.50	0.60	Poor
Test Model 9 against Model 8 (Can we exclude all second-order?)	>0.95	>0.95	0.95	>>0.95	Good
Test Model 10 against Model 8 (Can we exclude ATB x ATD?)	>0.95	>>0.95	>0.95	>>0.95	Good
Test Model 11 against Model 8 (Can we exclude DOSETOTAL x ATB?)	<0.10	<0.10	0.30	0.71	Poorer
Test Model 12 against Model 8 (Can we exclude all ATB?)	>0.95	>0.95	0.95	>>0.95	Good
Test Model 13 against Model 8 (Can we exclude DOSETOTAL x ATD?)	<0.10	<<0.10	0.10	0.30	Poorest
Test Model 14 against Model 8 (Can we exclude all ATD?)	>0.95	>>0.95	>0.95	>>0.95	Good
Test Model 15 against Model 8 (Can we exclude sex?)	>>0.95	--	--	--	Good
Test Model 16 against Model 8 (Can we exclude all DOSETOTAL?)	0.25	>0.95	0.73	>0.95	Mixed

[a] Level of significance = 0.05.

sex, and the various terms involving kerma. Table D-4 provides a summary of the predicted annual probability of death from stomach cancer for three possible ATB, with several different ATD, three kerma categories, and the two sexes, for five possible models. More complete tables are available on request. The numbers shown in the tables are in percent (100 times the mortality probability) for convenience of display.

The predicted mortality from stomach cancer is sensitive to ATB, ATD, and to sex. The probability depends also on the model, but in a complicated way. For example, the probabilities in Model 9 are much larger than those in the other models for people who were young at the time of bombing, but smaller for those who were older. Those are the effects of strong interaction terms. Notice also the varied effects of changes in DOSETOTAL. For young survivors, the effect of increasing the radiation is appreciable in some models, and always in the direction of increasing the probability of death. For older survivors, the effect of increasing radiation is small, sometimes decreasing the predicted probability of death. The negative coefficients in the higher-order terms (see Table D-2) cause these changes.

We also need to inquire whether the restriction to kerma of 0 to 299 rads has affected our results. We could have included observations corresponding to 300 to 399 rads or even 400 to 599 rads. Similar computations were carried out, including first one and then both of these additional kerma ranges. We paid particular attention to the coefficients of the linear and the quadratic terms of DOSETOTAL. The estimates of these coefficients decrease by as much as a factor of 2 for the models that fit well. In such cases, the fit is improved, and the conclusions about excluding the quadratic term or excluding the linear term are weakened slightly, but not changed.

The main object of our study is to estimate the assigned share (the probability of causation) for a person of a known age and sex who has cancer and suffered a specified dose of radiation at a given age. As

TABLE D-4

Probability of Death from Stomach Cancer in Year Predicted by Different Models

ATB	ATD	DOSE[a]	Probability, % Model for Males 5	6	8	9	11	Model for Females 5	6	8	9	11
4.5	11.5	0.0	0.0009	0.0009	0.0010	0.0089	0.0010	0.0004	0.0004	0.0005	0.0043	0.0005
		70.6	0.0013	0.0014	0.0012	0.0091	0.0012	0.0006	0.0006	0.0006	0.0044	0.0006
		142.4	0.0020	0.0021	0.0014	0.0092	0.0015	0.0010	0.0010	0.0007	0.0044	0.0007
	35.5	0.0	0.0125	0.0124	0.0129	0.0355	0.0130	0.0058	0.0058	0.0060	0.0171	0.0061
		70.6	0.0157	0.0164	0.0152	0.0361	0.0147	0.0074	0.0077	0.0071	0.0174	0.0069
		142.4	0.0210	0.0220	0.0180	0.0368	0.0167	0.0098	0.0103	0.0084	0.0177	0.0078
42.0	49.0	0.0	0.1207	0.1199	0.1189	0.0893	0.1178	0.0566	0.0562	0.0558	0.0431	0.0552
		70.6	0.1157	0.1200	0.1232	0.0909	0.1266	0.0542	0.0563	0.0578	0.0438	0.0594
		142.4	0.1170	0.1201	0.1277	0.0926	0.1364	0.0549	0.0563	0.0599	0.0446	0.0639
	73.0	0.0	0.5271	0.5235	0.5183	0.3556	0.5230	0.2477	0.2459	0.2435	0.1717	0.2457
		70.6	0.4956	0.5139	0.5248	0.3620	0.5127	0.2328	0.2414	0.2466	0.1748	0.2409
		142.4	0.4916	0.5043	0.5315	0.3687	0.5024	0.2310	0.2369	0.2497	0.1781	0.2360
65.0	72.0	0.0	0.4091	0.4065	0.4057	0.3666	0.4012	0.1921	0.1909	0.1905	0.1771	0.1884
		70.6	0.3689	0.3815	0.3822	0.3732	0.3948	0.1732	0.1791	0.1795	0.1803	0.1854
		142.4	0.3508	0.3577	0.3597	0.3801	0.3884	0.1647	0.1679	0.1689	0.1836	0.1824

[a]DOSETOTAL, rads kerma.

noted earlier (see Section VI D), the estimated assigned share depends on the model used, although the relative differences are not very large when the assigned share is greater than 10%. In fact, the differences between the predictions provided by different models are often much smaller than the difference from the predictions made by the Working Group using the modified BEIR III coefficients. The assigned shares estimated by some of our models turned out to be negative for some groups, especially those who were older at time of exposure. Thus, although the logit method guarantees that all the estimated probabilities of death must be between zero and unity, it does not require the estimated probability at zero exposure to be smaller than all other estimated probabilities. Owing to interaction terms and quadratic terms in kerma that have negative coefficients, the response surface is complicated and tends to be "wavy," although always above zero.

It is not clear what attitude should be adopted when assigned shares are estimated to be negative. One might say only that the estimated assigned share is well below 10%, so the fact that it is negative is not important. Another possibility is to proceed directly to the estimation of assigned share, rather than first estimating the various probabilities and then using them to get assigned share. From a statistical viewpoint, the latter procedure has advantages. We tried to estimate the response surface for assigned share in a fashion similar to that used to estimate probabilities. That is, we asked that the assigned share always be between zero and unity (between 0 and 100%) and that it increase slowly as kerma increases (on the average) and then more rapidly for larger kerma, finally leveling off. When and where the increases would take place were not specified, but left to the determination from the observations. The standard methods to accomplish this analysis, such as the logit method, will not provide a fit to the observations as they stand, because the reported number of deaths in the control sample (the zero-radiation sample) is often too high, giving a negative "observed" assigned share. It might be possible to smooth the observed values first, in that they come from a selected control sample in any case, but such manipulations seem

arbitrary now. It seems preferable to wait for the increased sample sizes that are already available and for the improved dosimetry.

A third possibility can be put forward. It is conceivable that negative assigned shares are real, even if they do not correspond to conventional thinking about biologic phenomena. In view of the uncertainties in the observations, the fact that the zero-radiation group is a selected sample, and the short period of observation that does not allow the observation of excess cancer deaths for most persons who were young at the time of exposure (small ATB), we cannot now come to such conclusions.

When additional data, especially incidence data, are available, we strongly urge that all the computations be carried out afresh, using estimation methods like the ones we have discussed or others that may prove informative.

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APPENDIX E

FORMULA FOR MULTIPLE DOSES

In Section III-E, the method for treating multiple exposures of a single person to radiation was discussed. If $E(d_o)$ and $E(d_m)$ are the excess risks corresponding to doses d_o and d_m rads, respectively, and $E(d_o,d_m)$ is the excess corresponding to $d_o + d_m$ rads, the Working Group assumed that

$$E(d_o,d_m) = E(d_o) + E(d_m). \tag{E-1}$$

The assumption was shown to be true whenever the total risk corresponding to dose $d = d_o + d_m$ satisfies

$$h(d) = h(0)\ (1 + \omega d), \tag{E-2}$$

where ω is a constant.

This appendix shows that the assigned share for dose d_o, when total dose $d = d_o + d_m$ was received, can be obtained from the standard tables by entering with a corrected dose d_c, such that

$$d_c = d_o/(1 + \omega\, d_m). \tag{E-3}$$

Note that the excess risk corresponding to dose d (given alone), E(d), is equal to h(d) - h(0), where h(d) is the risk corresponding to dose d. It follows directly from Equation E-1 that

$$h(d_o+d_m) = h(d_o) + h(d_m) - h(0). \tag{E-4}$$

Clearly, Equation E-4 is satisfied for the linear-risk model given in Equation E-2. However, it is easily verified not to hold for the

linear-quadratic dose-response model, which means that the Working Group's method would be inaccurate to the extent that the two doses led to a substantial quadratic response.

When Equation E-2 does hold, the AS corresponding to dose d, AS(d) equals

$$AS(d) = [RR(d) - 1]/RR(d)$$

$$= \omega d/(1 + \omega d), \qquad \text{(E-5)}$$

where $RR(d) = h(d)/h(0) = (1 + \omega d)$ is the relative risk corresponding to dose d relative to dose 0. In the presence of dose d_m, the AS for dose d_o, $AS(d_o:d_m)$, is

$$AS(d_o:d_m) = [RR(d_o+d_m:d_m) - 1]/RR(d_o+d_m:d_m)$$

$$= \omega d_o/(1 + \omega d_o + \omega d_m). \qquad \text{(E-6)}$$

This can be expressed as

$$AS(d_o:d_m) = \omega d_c/(1 + \omega d_c), \qquad \text{(E-7)}$$

where d_c is defined by Equation E-3. Thus, the usual tables of AS can be used to determine $AS(d_o:d_m)$ when Equation E-2 holds by first computing the adjusted dose d_c and then proceeding as before.

APPENDIX F

PROCEDURES USED BY THE WORKING GROUP TO CALCULATE ASSIGNED SHARES (PROBABILITIES OF CAUSATION)

In the main text, we commented on the ideas and methods used by the Working Group to calculate assigned shares (or, in its nomenclature, probabilities of causation, PCs). We now turn to the explicit details of the calculations for a person of sex s who received dose d at age t_0 and in whom a specified type of cancer was diagnosed at age t, which is $y = t - t_0$ years later.* The calculations apply to a U.S. inhabitant.

The details depend on the type of cancer and on the kind of radiation. We consider first an example for stomach cancer. Low-LET radiation of dose d was received at age $t_0 = 25$, and stomach cancer was diagnosed at age $t = 60$, which is 35 years later. What share is to be assigned to dose d of low-LET radiation? According to the Working Group, the assigned share or probability of causation is given by $PC = R/(1 + R)$, where R is the excess risk of cancer for such persons receiving dose d, compared with persons who did not receive any dose, that is, compared with the baseline risk. How is R to be calculated for stomach cancer as a function of d, t_0, t, and s? The details of the calculation require several assumptions, but, given those assumptions, each part can be explained. According to the Working Group, the excess relative risk, R, is given by

$$R = (d + d^2/116)TK,$$

where the factor $(d + d^2/116)$ is the simple multiplicative effect of low-LET radiation of dose d. This is the only place where the dose appears in the computations. This formulation is taken, following

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* The notation in this appendix follows that in earlier parts of this report, rather than that of the Working Group's draft final report.

BEIR-III, as linear-quadratic with a crossover dose of 116 rads for almost all types of cancer for low-LET radiation. We have commented earlier on the assumption of a single crossover dose independent of cancer type. The value of the crossover dose is based largely on observations of leukemia excess in Japanese atomic-bomb survivors.

The multiplicative term T adjusts for the fact that radiation does not produce cancer instantaneously. Given that a cancer was initiated by radiation received at age t_0, the probability that the cancer will have grown large enough to be diagnosed at age t depends on the number of years y that have elapsed and on the type of cancer. For all types of cancer other than leukemia and bone cancer, the factor T used by the Working Group is zero for the first 5 years after exposure and then increases to unity at 10 years after exposure through a cubic interpolation formula. This assumption is independent not only of cancer type but also of age at exposure and other variables. T may instead depend strongly on the type of cancer and especially on the age at which this type of cancer usually is diagnosed. Thus, T may depend not only on y but on t and on t_0, somewhat differently for each type of cancer and each sex.

The third factor, K, is the most difficult to explain, because it contains all the complications of type of cancer, age at exposure, sex, the excess in Japan, and the transfer from Japan to the United States. A fuller treatment may require the inclusion of age at diagnosis as well.

Perhaps the details of the factor K can be most easily explained by an example. Suppose we start with two groups of 100,000 baby boys born in, say, 1905. About 92,000 would still be alive in 1945. One group was exposed to radiation--say, in Hiroshima or Nagasaki--and their cancer incidence was studied over some period--say, 1950-1980, when they were aged 45 to 75. For some specific type of cancer--say, stomach cancer--the epidemiologists found no excess until 1955. They then counted cases through 1980 and, through some process of which we

are unsure, calculated that the annual excess risk per rad, e, averaged over the 25 years from 1955 to 1980, was 0.0508 per 100,000. (This number is taken from the 35-to-49 age group as tabulated in Table VI-1 of the Working Group's draft report. The Working Group actually interpolated the risk coefficients to values for each year of age at exposure, but the exact value is not important for this explanation.)

We wish to estimate the risks of radiation-induced cancer in the other 100,000 men born in 1905, as a function of time after exposure. (With only one birth cohort, we can estimate risks only for exposures at age 40. If we had started with a different birth cohort, we could do the analysis for the age that the cohort had attained in 1945.) In the constant-relative-risk model, the Working Group assumed that the excess risk of radiation-induced stomach cancer is proportional to the baseline risk that has been observed for these men. Let the baseline incidence rate be I(t) for age t. I(55), for example, is the number of cases of stomach cancer that occur in 100,000 men then living between their fifty-fifth and fifty-sixth birthdays. But not all the 100,000 baby boys have survived to age 55. A life table tells us that only a fraction of them, L(55) = 0.817, will still be living. Thus, between the ages of 50 and 75 (years 1955 to 1980), the number of baseline cancers, $N_b(50,75)$, expected in toto is the sum of the products of the baseline rates and the number of men still alive:

$$N_b(35,60) = \sum_{t=50}^{t=75} I(t)[100{,}000\ L(t)]. \qquad \text{(F-1)}$$

This sum uses discrete 1-year age steps. For some, it is easier to think in terms of integrals over continuous variables. If we make I(t) and L(t) continuous instead of discrete functions of t, then Equation F-1 becomes:

$$N_b(50,75) = 100{,}000 \int_{50}^{75} dt\ I(t)\ L(t)\ . \qquad \text{(F-2)}$$

In this form, the value of N_b is clearly the integral under a curve of I(t) x L(t) over the age period t = 50 to 75. Figure F-1 shows the functions I(t) and L(t) and their product. The integral that represents N_b is hatched. L(t) must decrease with age; I(t) usually increases with age, as shown.

Now suppose that all the living men in this group were exposed at age t_0 = 40 to 1 rad of radiation. What would be their excess cancer rate at a later age, t? According to the constant-relative-risk model, the excess risk Ex(t) is proportional to the baseline risk I(t). (The excess for larger doses depends on the dose-response relationship assumed. We do not need to consider that relationship for the present explanation.) Let us call the proportionality constant (for 1 rad) K:

$$Ex(t) = K\ I(t)\ . \qquad \text{(F-3)}$$

As for the baseline case, the number of radiation-induced cancers over a specified period can be calculated by applying the life table to adjust for the number of men alive and then integrating. We have deliberately taken the period of interest to be beyond the minimal latent period, so we can use a constant K. The number of radiation-induced cancers, $N_r(50,75)$, is

$$\begin{aligned} N_r(50,75) &= 100{,}000 \int_{50}^{75} dt\ Ex(t)\ L(t) \\ &= 100{,}000 \int_{50}^{75} dt\ K\ I(t)\ L(t) \\ &= K\ N_b(50,75). \end{aligned} \qquad \text{(F-4)}$$

How do we now estimate K? The Working Group notes that, if the first group of men (in our example, the Japanese ones) had all been exposed to 1 rad, their excess cancer rate, Ex(t:J), over the 25 years of observation would average e. (It does not count the first 5 years of observation or the 5 years before that, because no excess was

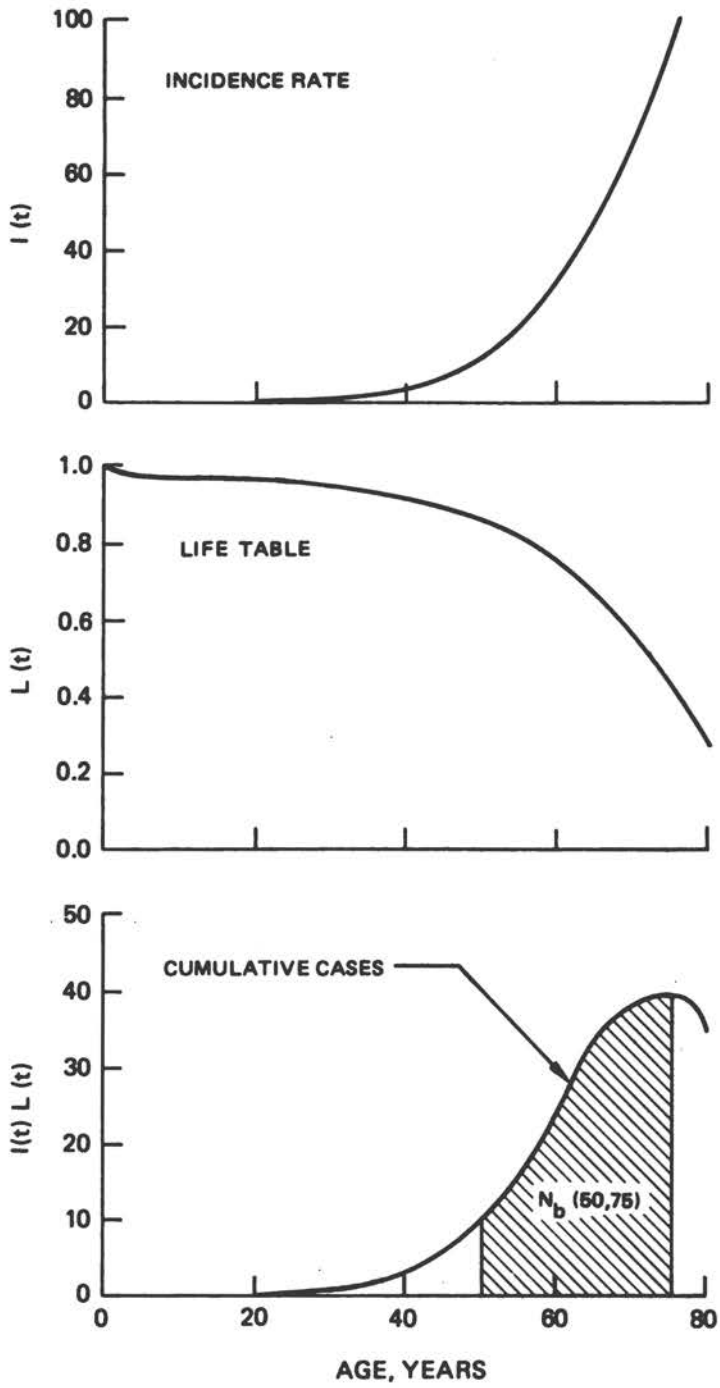

FIGURE F-1 Calculation of expected number of baseline cancers over fixed time.

observed over that entire period.) It then assumes that this same average absolute excess rate would apply to the second group over the same period.

In each year, 100,000 L(t) men would be at risk, so on average 100,000 e L(t) would get stomach cancer (see Figure F-2). The total number to get stomach cancer over the 25 years would be

$$N_r'(50,75) = \int_{50}^{75} dt\ 100{,}000\ e\ L(t)$$

$$= 100{,}000\ e \int_{50}^{75} dt\ L(t). \qquad \text{(F-5)}$$

We now have two estimates of the total number of people getting cancer over a given period, one from projecting the absolute excess from the first group to the second and one from assuming a constant-relative-risk model applied to the baseline risk in the second group. These two estimates, the Working Group argues, should give the same result over the observation period; only the distribution of cases over time during the period would differ. Thus,

$$N_r'(50,75) = N_r(50,75). \qquad \text{(F-6)}$$

Substituting from Equations F-4 and F-6,

$$100{,}000\ e \int_{50}^{75} dt\ L(t) = 100{,}000\ K \int_{50}^{75} dt\ I(t)\ L(t) \qquad \text{(F-7)}$$

or

$$K = e[\int_{50}^{75} dt\ L(t)]/[\int_{50}^{75} dt\ I(t)\ L(t)]. \qquad \text{(F-8)}$$

The Working Group uses the discrete form of Equation F-8

$$K = e\ [\sum_{t=50}^{t=75} L(t)]/[\sum_{t=50}^{t=75} I(t)\ L(t)]. \qquad \text{(F-9)}$$

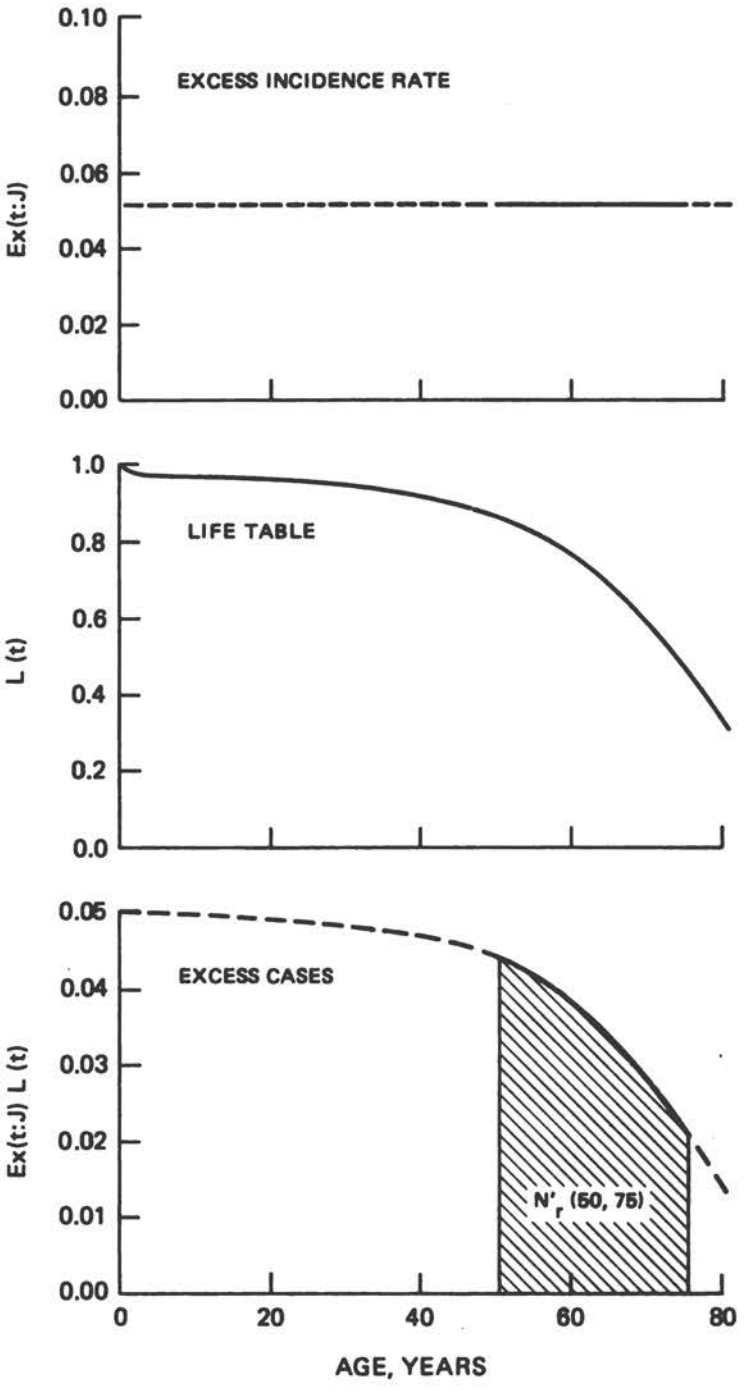

FIGURE F-2 Calculation of expected number of cancers assuming constant absolute risks over period of observation. Dashed lines indicate that extrapolation could be made, but is not needed.

Equation F-9 is essentially the same as the equation on p. 96 of the Working Group's July 1984 draft. (The terms of that equation were accidentally inverted. The coefficient e should be divided by the expression on the right, instead of multiplied by it.)

We can derive values of K for other ages at exposure by using the appropriate values of e and the appropriate periods of integration corresponding to the period of observation, as shown in Table VI-1 on p. 97 of the Working Group's July 1984 draft.

If we assume at the outset that the coefficient e--the average absolute excess risk over a stated period--is correct for the second population, we do not have to project from the first population to the second, and we do not need the first-described population of 100,000 baby boys. All we need do is observe that the cumulative excess risk must be the same, whether distributed uniformly at rate e or as a proportion K of the baseline risk over that specified time. That is probably why the Working Group does not mention Japanese risks in Chapter VI of its draft. The assumption about constant absolute excess risk among populations at risk is then subsumed in the derivation of the risk coefficient e and can be traced to BEIR III.

Several assumptions are needed to derive the factor K, as is evident in the example. The details of the smoothing of excess risk over the period from exposure to a designated year are not of great consequence, we presume, but it would be convenient to have the coefficients tabulated by year. Also, the U.S. life table that was used should be listed for each year of age; that life table apparently is split on sex but not on ethnicity. The use of the Working Group's Chapter VI would be clarified if the entries in its Table VI-1 were explained more fully--in particular, if the deviations from BEIR III were clearly indicated and the last columns were fully labeled. The column heading, "Years Follow-up," is not clear; the Oversight Committee believes that it refers to the number of years that the relevant study population (e.g., the atomic-bomb survivors) was observed.

The description of the detailed calculations applies to most cancer sites and low-LET radiation. The exceptions are as follows:

o Breast and thyroid cancer: The dose factor $(d + d^2/116)$ is replaced by d, that is, the radiation factor has a linear term only. The other details of the calculations are not changed.

o Leukemia and bone cancer: The dose factor is set at $(d + d^2/116)$, but the time factor, T, is changed, because leukemia and bone cancer have a short time of growth from exposure to diagnosis and because they are assumed to have a wavelike excess risk with time. The approximation for T comes from a log-normal distribution fitted to the observed distribution of specific cancers as a function of t_o, t, and sex. For leukemia, the distributions for acute leukemia and chronic granulocytic leukemia are combined with weights 0.68 and 0.32, corresponding to their relative frequency in the observed populations. Then the average excess risk is spread over the period under study according to the fitted log-normal distribution. The consequence is that T becomes greater than zero sooner after exposure and, in general, will eventually decrease when t becomes large, rather than remaining at unity, as occurs with other cancers. The calculation of K is also different, because the excess cancer risk due to radiation is not assumed to be proportional to the baseline risk taken from SEER, but is assumed to add to it. The total observed excess is spread over time, however, according to T, as we have just noted.

o High-LET radiation: For all types of cancer, the effect of increasing dose is taken as linear with high-LET radiation, but the increase is much more rapid with dose than with low-LET radiation. The dose factors adopted by the Working Group for d rads of high-LET radiation are 25 d for neutron radiation and 50 d for alpha radiation, except for breast and thyroid cancer, for which the functions are 10 d and 20 d, respectively. The other multipliers, T and K, are the same as for low-LET radiation.

APPENDIX G

THE RELATIONSHIP OF MECHANISMS TO DOSE-RESPONSE MODELS

No one knows the precise mechanisms of the induction of cancer in humans by radiation. In the case of experimental animals, enough is known to say that there is not a single mechanism by which all cancer is induced.[20,23] It is also clear that radiation can convert normal cells to potential cancer cells that may not express their malignant phenotype for a long time--and not until endogenous[22] or exogenous[19] factors provide the appropriate conditions for expression.

In the context of estimates of risk or assigned share, the question is whether knowledge about mechanisms can help to elucidate the dose-response relationships, and in particular help to choose the dose-response models that should be used.

Our knowledge of the mechanisms of induction and production of cancer, although deficient, implies that the contribution of various factors that influence the shapes of the dose-response curves will not be the same over a large range of doses. On a biologic and biophysical basis, changes both in the factors and in the degrees to which they contribute would be expected as the dose increases. Because many more data have been gathered at higher doses than at doses below 100 rads (1 Gy), they dominate the pragmatic curve-fitting. Any of the currently proposed models are very simplistic when applied to a given tumor, and the problem is compounded when a single model is selected for fitting data from several tumor types that involve very different factors.

The concern is to select appropriate dose-response curves that are plots of <u>incidence of specific cancers as functions of absorbed dose</u>. However, most of the available data or theories pertinent to the modeling of dose-response relationships concern the <u>initiation of potential cancer cells</u>. For example, is initiation a one-track or two-track event? Does it involve one or more gene loci?

There is little information on how the factors that affect expression influence the dose-response curves. The search is for a model that takes into account the factors that contribute to the probability, P, that a cancer will occur after exposure to radiation. That probability is the product of a number of contributing probabilities. A heuristic accounting of the factors of P might be as follows:*

$$P = P_t(1 - P_r)P_sP_e = F(d), \qquad (G\text{-}1)$$

where P_t = the probability that the targets involved in malignant transformation are hit,

$(1 - P_r)$ = the probability that the transformation events (probably mutations) or the lesions that lead to these events are not repaired (or not repaired correctly),

P_s = the probability that a malignantly transformed cell survives,

P_e = the probability that expression of the transformed or initiated cell occurs, including growth to an overt cancer in the lifetime of the person, and

d = dose, in rems, taking into account dose rate, fractionation, and radiation quality.

F(d) indicates that P is a function of the dose, d. Equation G-1 is based on the assumption that tumors are of monoclonal origin.[2] If, as has been suggested in some cases, more than one cell has to be involved to produce a cancer,[10,13-15,24,25] a quadratic term must be included in the formulation of the response.

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* With acknowledgment to H. I. Kohn,[7] who suggested this approach to examining the probability of genetic effects from radiation.

Experimental evidence suggests that the mechanisms of the induction of different tumor types are distinct and that one dose-response model will not be adequate to describe the responses of various tissues. The selection of a single model is arbitrary and a matter of judgment. What, then, do we know about mechanisms that can at least guide us in the selection of a model or method of estimating the effect over a wide range of doses?

Radiobiologists concerned with the mechanisms of cancer initiation suggest that it may require two or more independent changes (hits or events) in the genome. If the probability of each of, say, N independent events is linearly related to radiation dose, a term in the initiation probability (P_t) that is proportional to the Nth power of dose might be expected. This reasoning has been used to justify a term quadratic in dose in the overall dose-response relationship for radiation-induced cancer, starting with the assumption that two dose-dependent events must occur to initiate it (N = 2). For example, two sites in DNA might need to be damaged within a short time, and, with low-LET radiation, two tracks of ionization would usually be needed. A linear response would be observed if the sites were sufficiently close to be affected by a single track or if one event (more generally, N - 1 events) were inherited, resulted from exposures to other agents, or resulted from other exposures to radiation. Thus, only a single-track event would be required to complete the initiation. Such a scenario assumes that the inherited or induced changes are not repaired. Linearity would not hold if the sequence of events were important; that would violate the independence assumption.

A further hypothesis is that the entire process of carcinogenesis entails multiple stages, whether or not it requires multiple events for initiation. The idea of multistage mechanisms is old,[3] but popular. For example, in the heuristic accounting, there would be an initiation stage accounted for by P_t, a (potential) repair stage accounted for by P_r, a survival stage accounted for by P_s, and a promotion or expression stage accounted for by P_e. If the probabilities for more

than one of the stages depended on dose, the potential for quadratic or higher-order terms in the overall dose-response relationship would arise. Again, the relationship might appear linear in dose if other factors such as inherited defects or other agents also could affect the stages affected by radiation.

What are the arguments for and against observing a linear response in an exposed human population, accepting for now that either multiple events or multiple stages are required? For extended exposures to chemical carcinogens, Schoenfelder and Hoel[17] have argued that, even when two mutation-like initiating events are required, dose-response relationships may be linear. Some scientists suggest that an analogous situation may occur with radiation. However, linearity seems to require relatively stable changes induced naturally or by other agents. If stable changes occur, one might expect the number of such changes to increase with age and therefore the susceptibility to radiation-induced cancer to increase. It is certainly not a general rule that susceptibility increases with age; in fact, the evidence is just the opposite for breast, lung, and stomach cancers[4,22] and sarcomas.[5] However, it has been suggested that the risk of leukemia may be greater in the very young and the elderly.[11,18] For the special assumption that some people have inherited all but one event, any estimate of the contribution of radiation would have to be assessed by comparison with a genetically appropriate nonexposed population, not with the general population.

Evans[1] suggested that one might observe a "practical threshold" in the case of bone tumors in the radium-dial painters, because, even though initiation might occur without a threshold, with low doses the latent period might exceed the life expectancy. Other interpretations favor a linear model for bone cancer,[9] however, and dose-response models that include a threshold have been dismissed, by and large, for the induction of cancer in humans.

What experimental evidence supports the hypothesis that cancer initiation requires two or more events? Recent studies have suggested that at least two gene loci are involved in malignant transformation in vitro.[8] The target for radiation thus would be large, and the response would be quadratic, because two independent single-track events would be required. If the order in which the genetic changes must occur is important, an even higher power of dose might be required in the model. If the loci are close enough at some times in the cell cycle, a single track might affect both loci, and a linear term might be needed as well. Because of the nature of the tracks, such single-track events would be more probable for radiation of higher LET.

If carcinogenesis also occurs through chromosomal breaks and translocations, molecular biology indicates a large target and therefore argues against a single-track event with low-LET radiation. Some evidence now indicates that specific chromosomal translocations involving movement of c-onc genes may be associated with a number of human and murine lymphomas.[6,12,21] The association of chromosomal aberrations with specific oncogene activation is an attractive idea,[16] especially to students of radiation effects, but the critical experiments to establish the precise relationship remain to be done.

In summary, the contributions of various factors to the shape of the dose-response curves for radiation-induced cancer vary with dose. That fact and the multiplicity of factors involved indicate that current models for estimating risk constitute, at best, a first approximation. Whether a cancer results from exposure to radiation depends on a conglomerate of probabilities that range from the probability of the inheritance of specific genes to the probability of exposure to other cancer-initiating agents. Recent advances in the understanding of possible mechanisms of cancer induction point to the need to damage two or more targets that are probably separated by considerable distances for most of the cell's history. If two targets are involved, then purely linear dose-response models for the induction of cancers by low-LET radiation seem implausible. Yet it has been

argued that special circumstances will produce linear responses, even when two initiating events or two dose-dependent stages are necessary.

As stated earlier, future revision of the tables must take into account any information that bears on the influence of radiation dose and dose rate on the risk of cancer. Mechanistic considerations can help in determining which of the possibilities allowed by the data are most plausible.

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APPENDIX H

ASSIGNED SHARE AND MEDICAL PRACTICE

A second primary cancer of the same or different histologic type may occur some years after the apparently successful radiation treatment of an earlier cancer.[1] In considering the likelihood that therapeutic radiation would be followed by the appearance of a second cancer some years later, could the treating physician be considered liable for inducing the second neoplasm if a nonzero assigned share could be calculated?

Persons undergoing therapeutic radiation have an increased incidence of later neoplasms, most often in or near the sites of the irradiated lesions.[5,7,10-12] The papers just cited could be interpreted as suggesting that medical radiation is causative. Tables I-1 and I-2, from Boice,[1] indicate populations studied for later neoplasms after radiation therapy for benign and malignant diseases.

There are also reports of increases in carcinogenic effects due to medical diagnostic radiation exposure. The use of thorium dioxide (thorotrast) as a contrast agent in radiographic procedures between 1930 and 1955 has led to excess mortality from liver cancer and acute leukemia. Women who received multiple chest fluoroscopic examinations to monitor pneumothorax treatment for pulmonary tuberculosis are at increased risk of breast cancer. Apart from these examples, however, epidemiologic studies of medical diagnostic radiation exposures and of the use of diagnostic radionuclides, such as iodine-131, have generally not demonstrated an increased risk of leukemia or other forms of cancer in exposed patient populations.[2,3,8,9]

The use of adjuvant chemotherapy for cancer, with or without radiation therapy, as in the treatment of patients with Hodgkin's disease and the non-Hodgkin's lymphomas, has been associated with an increased risk of acute nonlymphocytic leukemia.[4,6] These reports

TABLE I-1

Studies of Populations Irradiated for Benign Disease[a]

Treatment for	Excess Cancers
Ankylosing spondylitis	Leukemia, lymphoma, lung, pharnyx, stomach, pancreas, bone, others
Postpartum mastitis	Breast
Thymus hypertrophy	Thyroid
Tinea capitis	Thyroid, brain
Benign head and neck disease	Thyroid
Metropathia hemorrhagica	Leukemia, intestine, rectum, uterus

[a] Reprinted with permission from Boice.[1]

TABLE I-2

Studies of Populations Irradiated for Malignant Disease[a]

Treatment for	Excess Cancers
Cervical cancer	No leukemia, possibly bladder, rectum, uterus
Childhood cancer	Other cancers or sarcomas
Hodgkin's disease	Leukemia, non-Hodgkin's lymphoma
Ewing's sarcoma	Osteosarcoma
Retinoblastoma	Osteosarcoma
Ovarian cancer	Bladder, colon

[a] Reprinted with permission from Boice.[1]

indicated that chemotherapeutic agents, particularly alkylating agents, appear to have a greater leukemogenic potential than radiation.

Many of the irradiated populations would not have the same baseline cancer rates as the general population, even if one discounted their primary cancer; they often have an increased risk of a second cancer. Patients whose radiation exposure is diagnostic, rather than therapeutic, are also different from the general population to some degree. Thus, in many instances of medical radiation, tables of assigned shares based on radiation risk factors and baseline rates in the general population would not apply to the irradiated population, because of selection factors other than radiation.

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GLOSSARY

This glossary defines terms in the report that are likely to be unfamiliar to some readers or that are used in special ways. They are often defined with reference to radiation, cancer, and assigned shares, but many of them also have more general meanings.

Absolute risk Expression of excess risk due to exposure as the arithmetic difference between the risk among those exposed and the risk among those not exposed.

Absorbed dose The quantity of energy imparted to matter by ionizing radiation per unit mass of irradiated material at the site of interest. Units: rad and gray (Gy). 1 gray = 100 rads.

Acute exposure Radiation exposure of short duration.

Additive risks Used to describe the situation in which the total absolute risk from two or more factors considered together is equal to the sum of the absolute risks from the factors considered individually.

Age-specific Applies to cancer incidence or mortality rates over specific age intervals, rather than cumulated, averaged, or age-standardized over a lifetime.

Alpha particle A charged particle emitted from atomic nucleus, with mass and charge equal to those of helium nucleus: two protons and two neutrons; a doubly charged helium ion.

Ankylosing spondylitis Rheumatoid arthritis of the spine, a chronic inflammatory disease involving intervertebral joints that often leads to fusion of vertebrae; more common in males.

Assigned share For two groups of people that are alike, except that one group is exposed to a specific dose of radiation and the other is not exposed, the excess number of cancer cases in the exposed group expressed as a fraction of the total number of cancer cases in the exposed group is called the assigned share for the exposure. This fraction may be assigned to each person with cancer in the exposed group.

Association The occurrence together of two or more characteristics or events more often or less often than would be expected by chance.

Ataxia telangiectasia A hereditary, progressive disorder involving the eyes, skin, central nervous system, and small blood vessels; patients have an increased risk of cancer, especially leukemia and lymphoma, and have increased chromosomal abnormalities and radiosensitivity of cells.

Attributable risk The extent to which the incidence of a disease can be explained by or attributed to the characteristic or risk factor under study. Such a measure can be applied to the general population or to exposed persons only. (When applied to exposed persons only, in the case of radiation, it is essentially equivalent to assigned share.)

Background radiation Radiation arising from radioactive material other than that under consideration; background radiation due to cosmic rays and natural radioactivity is always present; background radiation may also be due to the presence of radionuclides in building materials, etc.

Baseline As applied to cancer incidence or mortality, the frequency of cancer that a population would experience, given its personal characteristics and geographic location, without exposure to radiation other than background radiation.

BEIR Committee National Research Council Advisory Committee on the Biological Effects of Ionizing Radiations.

BEIR III The BEIR Committee that produced the report, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980.

Beta particle Charged particle emitted from the nucleus of an atom, with mass and charge equal to those of an electron.

Cell inactivation The loss of reproductive capacity of a cell as a result of exposure to an agent, such as radiation. Inactivated cells cannot proliferate, so it is assumed that cell inactivation after exposure to high doses of radiation reduces the risk of cancer. With respect to its effect on carcinogenesis, it is equivalent to cell-killing.

Chronic exposure Radiation exposure of long duration.

Cohort Any designated group of persons who are followed or traced over a period, such as those exposed to radiation and of known age and sex.

Competing causes In a study of cancer mortality or incidence related to radiation, any factors other than radiation that could cause specific outcomes or specific types of cancer.

Competing-risks model A model for the analysis of survival data that uses mutually exclusive competing causes.

Confidence limits of the mean The range of possible values within which the sampled population's mean is likely to lie. Confidence limits for a sampled population are calculated using the mean, standard deviation, and size of the sample. If a confidence limit is 95%, one can say with 95% confidence that the sampled population's mean lies within this range. Thus, 95% of such statements are correct.

Confounding variable A variable whose values differ between the study group and the control group and that affects the outcome being assessed.

Control group A population or sample of a population that is used for comparison with a study group. Ideally, the control group is identical with the study group in all its characteristics except that it does not possess the characteristic under study or has not been exposed to the treatment under study.

Cumulative dose Total dose resulting from repeated exposure to radiation.

Dose A general term denoting the quantity of radiation or energy absorbed; for special purposes, it must be qualified; if unqualified, it refers to absorbed dose.

Dose equivalent (abbr., DE) The quantity that expresses amounts of all kinds of radiation on a common scale for calculating the biologically effective absorbed dose; the product of the absorbed dose in rads and modifying factors. Units: rem and sievert. 1 sievert = 100 rems.

Dose rate The quantity of absorbed dose delivered per unit time.

Dose-response relationship The mathematical relationship between the radiation dose absorbed in a given organ or tissue and the biologic response or risk (e.g., cancer incidence or mortality). Often expressed as an algebraic equation or a graph defining the response as a function of dose.

Excess The number of cancers occurring in excess of the baseline or expectation.

Exposure Generally, the state of receiving energy from ionizing radiation. Technically, measured in terms of the ionization produced in air by x or gamma radiation; it is the sum of the electric charges of one sign produced in air when all electrons liberated by photons in a volume of air are completely stopped in air, divided by the mass of air in the volume. Unit: roentgen (R).

External radiation Radiation from sources that are outside the body, such as the initial radiation from the Hiroshima and Nagasaki bombs and fallout from nuclear weapons tests.

Extrapolation The use of information gathered under one set of conditions to predict results under a different set of conditions, usually involving a quantitative difference in some factor, such as dose or time.

Fluoroscopy Use of an x-ray machine with transfer to a fluoroscopic screen of the image of part of the body for diagnostic purposes.

Fractionation The division of a dose of radiation into relatively small doses given daily or at longer intervals, usually at high dose rate.

Gamma rays Short-wavelength electromagnetic radiation of nuclear origin (range of energy, 10 keV to 9 MeV).

Genome The DNA content of a cell.

Gray (abbr., Gy) SI unit of absorbed dose of radiation; 1 Gy = 100 rads.

Hazard function The mathematical function that represents the dependence of the incidence (or mortality) rate for a cancer on such variables as extent of exposure, time after exposure, and age.

High-LET radiation Protons, neutrons, and alpha particles. (See Linear energy transfer.)

ICRP International Commission on Radiological Protection.

Incidence (rate) The rate of occurrence of a disease within a specified period; usually expressed as number of cases per 100,000 or per million per year. An approximation of the risk of developing a given disease, calculated as the ratio of the number of persons who develop the disease over a stated period to the number of persons in the population at the midpoint of the period.

Initiation The postulated first step in carcinogenesis. It is irreversible. Most initiating agents are mutagens. (See Promotion.)

Internal radiation Radiation from a source within the body (as a result of deposition of radionuclides in tissue, such as radon and its decay products inhaled by uranium miners).

Ion Atomic particle, atom, or chemical radical bearing an electric charge, either negative or positive.

Ionization The process by which a neutral atom or molecule acquires a positive or negative charge.

Ionizing radiation Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter.

Kerma Kinetic energy released in material. A unit of quantity that represents the kinetic energy transferred to charged particles per unit mass of irradiated medium when indirectly ionizing (uncharged) particles--i.e., photons or neutrons--traverse the medium. Units: ergs/gram, joules/kilogram, rads, and grays.

Latent period Period of seeming inactivity between time of exposure of tissue to an injurious agent and an observable effect, such as diagnosis of cancer.

LET See Linear energy transfer.

Linear dose-response relationship The dose-response relationship in which the response is proportional to dose and increases with increasing dose, the coefficient is positive, and there is no threshold of dose for the effect.

Linear energy transfer (abbr., LET). The average amount of energy lost per unit of particle track length. Average is specified because secondary particles set in motion by photon or neutron beams are not all of the same energy and because a particle near the end of its path loses energy at a higher rate.

Linear-quadratic dose-response relationship The dose-response relationship in which the response increases with increasing dose as a weighted sum of terms linear and quadratic in dose; in the low-dose region, the response is approximately linear and there is no threshold of dose for the effect.

Locus A specific place on a chromosome associated with a specific gene.

Low-LET radiation X rays, gamma rays, and electrons. (See Linear energy transfer.)

LSS Life Span Study of the Japanese atomic-bomb survivors; sample consists of 109,000 persons, of whom 82,000 were exposed to the bombs, mostly at low doses.

Mastitis Inflammation of the mammary gland.

Mechanism Any fundamental physical, chemical, or biologic process that is thought to be involved in the development of a cancer from radiation or other influences.

Medical exposure Exposure to ionizing radiation in the course of diagnostic or therapeutic procedures; as used in this report, includes diagnostic radiology (e.g., the use of x rays), exposure to radioisotopes in nuclear medicine (e.g., the use of iodine-131 to treat hyperthyroidism), external therapeutic irradiation (e.g., with cobalt for cancer), and dental radiation exposure.

Melanoma A tumor made up of melanin-pigmented cells; unless otherwise specified, it is considered to be malignant.

Model A mathematical formulation that incorporates assumptions about how cancer rates vary with defined variables, such as dose and age; used to predict rates and compute assigned shares.

Monoclonal Stemming from a single cell.

Morbidity Generally, the condition of being diseased. Quantitatively, the ratio of sick to all persons in a community.

Mortality The number of deaths attributed to a specific cause--e.g., a type of cancer--as the underlying cause of death in a defined population in a defined period, often expressed as number of deaths per 100,000 or per million persons per year.

Multiple myeloma Plasma cell myeloma; an uncontrolled proliferation of malignant plasma cells in the bone marrow.

Multiplicative risks Used to describe the situation in which the total relative risk from two or more factors considered together is equal to the product of the relative risks from the factors considered individually.

Murine Relating to the mouse genus Mus.

NCRP National Council on Radiation Protection and Measurements.

Neoplasm Any new and abnormal growth, such as a tumor, whether malignant or benign.

Odds ratio A measure of the strength or degree of an association, measured as the odds of having the risk factor if a given condition is present divided by the odds of having the risk factor if the condition is not present.

Oncogene A gene that, when expressed, may play a role in carcinogenesis.

Partition The classification of people or objects into mutually exclusive and exhaustive groups; the set of groups created by such a classification.

Person-rem (synonym, man-rem) A unit of population exposure obtained by summing individual dose-equivalent values for all people in the population. Thus, the number of person-rems contributed by 1 person exposed to 100 rems is equal to that contributed by 100,000 people each exposed to 1 mrem.

Person-year A unit of epidemiologic analysis computed by adding the numbers of years of observation of each member of a group being studied. Numbers of person-years specified by age, sex, and calendar period can be used to estimate expected numbers of baseline cancers in a population.

Plateau A period of above-normal, relatively uniform incidence of morbidity or mortality in response to a given biologic insult.

Probability of causation In this report, synonymous with assigned share.

Projection Use of the cancer experience in one population to predict that in another.

Promotion A postulated later stage of carcinogenesis after initiation required for the expression of a cancer. Promoters are by definition not carcinogenic alone, nor are they mutagenic, but they cause more cancer to occur than in their absence. Promotion is reversible. (See Initiation.)

Protraction The spreading out of a radiation dose over time by continuous delivery at lower rates over a period constituting a sizable fraction of the life span and long enough for age-dependent changes in susceptibility to occur.

Quadratic dose-response relationship The dose-response relationship in which the response increases as a quadratic function of increasing dose and there is no threshold of dose for the effect.

Quality factor (abbr., QF) The LET-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses the biologic effectivess of an absorbed dose on a common scale for all kinds of ionizing radiation. QF is the multiplying factor that converts absorbed dose in rads or grays to a dose equivalent in rems or sieverts.

Rad Unit of absorbed dose of radiation; 1 rad = 0.01 J/kg = 100 ergs/g.

Radiation The emission and propagation of energy through matter in the form of waves, such as electromagnetic waves, or particles, such as alpha and beta particles.

Radiation Effects Research Foundation. (abbr., RERF) Japanese foundation, chartered by the Japanese Welfare Ministry under an agreement between the United States and Japan, that studies the health experience of the survivors of the atomic bombs in Hiroshima and Nagasaki; successor to Atomic Bomb Casualty Commission (ABCC).

Radiation quality Indicates the magnitude of the LET of a given type of radiation; sometimes refers to the degree of penetration of a beam of x rays or gamma rays.

Radioactivity The property of some nuclides of spontaneously emitting particles or gamma rays, of emitting x rays after orbital electron capture, or of undergoing spontaneous fission.

Radioepidemiologic Refers to the study of the health effects of radiation in a group of exposed persons.

Ray See specific type--alpha, beta, gamma, or x.

RBE: See Relative biologic effectiveness.

Reasonable medical probability The situation when a medical expert believes that the likelihood that a disease or injury has been caused by some previous act or agent exceeds 50%.

Relative biologic effectiveness (abbr., RBE) A factor used to compare the biologic effectiveness of absorbed doses of different types of ionizing radiation; more specifically, the experimentally determined ratio of an absorbed dose of a standard reference radiation to the absorbed dose of the radiation in question required to produce an identical biologic effect in a particular experimental organism or tissue. Thus, if 3 rads of 200-kVp x rays equaled in lethality 1 rad of fast neutrons, the RBE of the fast neutrons would be 3. Quality factors are a subset of RBE factors defined for use in radiation protection. (See Quality factor.)

Relative risk The probability of developing a disease if a given risk factor is present divided by the probability of developing the disease if the risk factor is not present; a measure of the strength or degree of association applicable to epidemiologic and experimental studies.

Rem A unit of dose equivalent: the product of absorbed dose (in rads), quality factor, and any other necessary modifying factors; represents the quantity of radiation that is equivalent--in biologic damage of a specified sort--to 1 rad of 250-kVp x rays.

RERF Radiation Effects Research Foundation.

Risk A general term describing the probability of developing or dying from a condition or disease. Can be used in a restrictive sense to mean the probability of developing a cancer within a defined period after exposure to radiation.

Risk allocation The process of deciding how cancers that developed would be distributed according to cause or time after exposure, given an estimate of the total number of cancers over a stated period.

Risk factor An attribute or exposure (for example, to radiation) that has been shown to be associated with an increased odds ratio or relative risk of developing a condition or disease; does not necessarily imply cause-and-effect relationship, but in this report implies that the risk factor precedes the development of the condition or disease.

Roentgen (abbr., R) A unit of exposure; 1 R = 2.58×10^{-4} coulombs/kg of air.

SEER Surveillance, Epidemiology, and End Results program of the U.S. National Cancer Institute.

Selection bias An error in assignment that occurs whenever the selection of study and control subjects produces a difference between the groups that affects the results of the study.

Sievert (abbr., Sv) SI unit of radiation dose equivalent; 1 Sv = 100 rems.

Smoothing The process of avoiding discontinuity of risk estimates by using statistical techniques that account for continuous variations in such factors as age and radiation dose.

Solid cancers Cancers of non-blood-forming tissue, such as lung, breast, or bone.

Stochastic Describes effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) is a direct function of dose; these effects are commonly regarded as having no threshold.

Target The specific part of a cell or tissue that can be damaged by radiation.

Threshold dose An absorbed dose below which it is postulated that no effect (e.g., cancer) will be induced.

Tort law The body of law that governs civil actions involving battery, negligence, or strict liability. To establish a claim under tort law, it is necessary to demonstrate proximate cause. Conventionally, claims of injury are resolved in court under tort law.

UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation.

Working level (abbr., WL) Any combination of radon daughters in 1 liter of air that will result ultimately in the emission of 1.3×10^5 MeV of potential alpha energy.

Working-level month (abbr., WLM) Exposure resulting from inhalation of air with a radon-daughter concentration of 1 WL for 170 working hours.

Workman's compensation In contrast with tort law, a method of compensating a worker for an injury as determined by workman's compensation boards, usually with fixed compensation depending on the extent of injury; a no-fault system administered by the states. The acceptance of workman's compensation precludes a suit directed against the employer.

X ray Penetrating electromagnetic radiation whose wavelength is shorter than that of visible light; usually produced by bombarding a metallic target with fast electrons in a high vacuum; in nuclear reactions, it is customary to refer to photons originating in the nucleus as gamma rays, and those originating in the extranuclear part of the atom as x rays.

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