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Executive Director
Commission on Life Sciences

November 21, 2000

Dr. Charles E. Land
Section Chief
Radiation Epidemiology Branch
National Cancer Institute
EPS 7046
6120 Executive Boulevard, MSC 7238
Bethesda, MD 20892

Dear Dr. Land:

On behalf of the Commission on Life Sciences and the Board on Radiation Effects Research, I am pleased to enclose a "PREPUBLICATION" copy of *A Review of the Draft Report of the NCI-CDC Working Group to Revise the "1985 Radioepidemiology Tables."* **The report is not for public release until Wednesday, November 29, 2000, 10:00am EST**. This report is in response to a request under DHHS contract 200-95-0965, with the Centers for Disease Control and Prevention, for the National Research Council's (NRC) Subcommittee to Review the Radioepidemiology Tables to review the draft report of the NCI-CDC working group charged with revising the 1985 radioepidemiololgic tables.

Sincerely

Warren R. Muir, Ph.D.
Executive Director

Enclosure: 1 copy of report ("PREPUB")

cc: F. Owen Hoffman, SENES Oak Ridge Inc.
~~Ersie Farber, Department of Veterans Affairs~~

2101 Constitution Avenue, NW, Washington, DC 20418 *Telephone* (202) 334 2500 *Fax* (202) 334 1639 national-academies.org

ADVANCE COPY

NOT FOR PUBLIC RELEASE BEFORE

Wednesday, November 29, 2000
10:00 a.m. EST

PLEASE CITE AS A REPORT OF THE
NATIONAL RESEARCH COUNCIL

A Review of the Draft Report of the NCI-CDC Working Group to Revise the "1985 Radioepidemiological Tables"

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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 to appropriate balance.

This report was prepared under the Centers for Disease Control and Prevention contract 200-95-0965 between the National Academy of Sciences and the Centers for Disease Control and Prevention.

International Standard Book Number 0-309-07250-6

A limited number of copies of this report are available from the:
National Research Council
Board on Radiation Effects Research
2101 Constitution Avenue, NW
Washington, DC 20418
(202) 334-2232

Printed in the United States of America

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DUNCAN C. THOMAS, University of Southern California, Los Angeles, CA
DANIEL WARTENBERG, Robert Wood Johnson Medical School, Piscataway, NJ
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CLS ADVISER
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†Member of IOM

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PREFACE

The National Research Council's Committee on the Assessment of the Centers for Disease Control and Prevention's Radiation Programs was called on to review the draft report of the NCI-CDC working group charged with revising the 1985 radioepidemiological tables. This report provides an assessment of the utility of the data sources used by the working group in their preparation of the revised tables, evaluation of the assumptions implicit in these tables concerning radiologic effects, the epidemiologic and biostatistical methods used in these tables and the means by which uncertainties were handled, and provides advice regarding how these tables should be made available to the public.

The subcommittee members wish to thank the members of the working group who have contributed to their understanding of the revised tables and to their work. Drs. James M. Smith and Charles Miller of CDC provided a valuable perspective on the activities of the Radiation Studies Branch and useful historical insights for the subcommittee's study. Drs. Charles Land and Ethel Gilbert, of the Department of Health and Human Services (DHHS-NIH), and Owen Hoffman, Iulian Apostoaei, and Brian Thomas of SENES Oak Ridge, Inc., were generous with their time and thorough in discussing the strategy adopted in the revision of the radioepidemiological tables and in demonstrating the interactive computer program developed for computation of assigned shares. The subcommittee is especially grateful for the information provided by Dr. Neil Otchin, a representative of the Department of Veteran Affairs.

The subcommittee thanks the National Research Council staff who worked with us, especially Dr. Isaf Al-Nabulsi for keeping the subcommittee focused and preparing several drafts of this report. She was well assisted in the administrative details related to the subcommittee's work by Bridget R. Edmonds and Doris E. Taylor.

William J. Schull
Chairman

ACKNOWLEDGEMENTS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their participation in the review of this report:

John D. Boice, International Epidemiology Institute, Rockville, MD
Shirley A. Fry, Oak Ridge, TN
Donald E. Jose, West Chester, PA
Kenneth J. Kopecky, Fred Hutchinson Cancer Research Center, Seattle, WA
Stephen Lagakos, Harvard University, Boston, MA

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by David G. Hoel, appointed by CLS, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring subcommittee and the institution.

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EXECUTIVE SUMMARY

The National Research Council was asked by the Centers for Disease Control and Prevention (CDC) to review the draft report of the National Cancer Institute (NCI)-CDC's working group charged with revising the 1985 radioepidemiological tables. To this end, a subcommittee was formed consisting of members of the Council's Committee on an Assessment of the Centers for Disease Control and Prevention Radiation Programs and other experts. The original tables were mandated under Public Law 97-414 (the "Orphan Drug Act") and were intended to provide a means of estimating the probability that a person who developed any of a series of radiation-related cancers, developed the cancer as a result of a specific radiation dose received before the onset of the cancer. The mandate included a provision for periodic updating of the tables. The motivation for the current revision reflects the availability of new data, especially on cancer incidence, and new methods of analysis, and the need for a more thorough treatment of uncertainty in the estimates than was attempted in the original tables. The subcommittee discusses this point in more detail in section 10.

The working group has chosen to replace the 1985 tables with an interactive computer program [Interactive Radio-Epidemiological Program (IREP)]. Their stated aim has been to provide agencies and individuals with a means of computing estimates of cancer risk after exposure to radiation that reflect the circumstances of an individual compensation claim better than was possible with the original tables and of ascertaining the statistical uncertainty inherent in a particular estimate of radiation-related assigned shares.[1] The subcommittee believes that this approach provides a broader coverage of cancer sites of potential interest to individual claimants than did the 1985 tables, and that the accompanying computer program could have wide applicability. The working group deserves considerable praise for its efforts, not only with regard to the specific mandate, but also with regard to a broader understanding of the policy

[1] The calculated probabilities pertain to populations rather than individuals and as such are not probabilities in the usual sense, but are properties of the group to which a person belongs. These probabilities are assigned to a person for the purposes of compensation, and the term assigned share is used to emphasize the difference.

context of the mandate. The interactive software offers many advantages over the tables that it supplements, and there has clearly been careful thought regarding IREP's implementation.

However, considerable development work will be needed before this product will be suitable for any but highly specialized audiences. Although the subcommittee endorses the working group's approach, in part because of its greater flexibility, we do not believe that a computer program should replace the printed tables; the latter are potentially more useful to members of minority groups and economically disadvantaged groups who do not have access to computers.

The subcommittee concludes that the working group has done an excellent job of selecting data sources on which to base its model of assigned shares and has made reasonable judgments in selecting values of the model parameters and characterizing their uncertainties. However, there is a need to clarify the sources of information on uncertainty with regard to the relative biological effectiveness of various qualities of radiation, the dose and dose-rate effectiveness factor, and the miscellaneous other factors that possibly influence risk. More thought should be given to the inclusion in the model of a systematic risk factor for persons with known genetic radiosensitivity predispositions. Moreover, the subcommittee was concerned about the problems with including so many cancer sites for which radiation associations have not been well established. In such circumstances, subjective confidence intervals can be very wide and could lead to a situation in which compensation is awarded under dubious conditions of causation while a scientifically stronger case with a narrow confidence interval fails. The validity of this approach should be carefully considered. The subcommittee further recommends that the working group clearly describe and discuss in the report the changes in risk estimates and uncertainty ranges from the 1985 to the 2000 tables and the likely impact of these changes on compensation claims.

1. INTRODUCTION

On April 18, 2000, the National Research Council was asked by the Centers for Disease Control and Prevention (CDC) to review the draft report of the National Cancer Institute (NCI)-CDC's working group charged with revising the 1985 radioepidemiological tables. To this end, a subcommittee was formed consisting of members of the Council's Committee on an Assessment of the Centers for Disease Control and Prevention Radiation Programs and other experts. The proposed study began in May 2000. The goal was to produce a consensus report by August 23, 2000. A slate of subcommittee members was developed that contained nine nominees (the chair and four members of the parent committee and four new members) with expertise in epidemiology, risk assessment and risk communication, computational modeling, and statistics (especially in uncertainty analysis). The tasks set before the subcommittee were (1) to assess the utility of the data sources used by the radioepidemiological tables working group in its preparation of the revised tables, (2) to evaluate the assumptions implicit in the tables concerning radiologic effects, (3) to consider the epidemiologic and biostatistical methods used in the revision, (4) to appraise the means by which uncertainty was handled, and (5) to provide advice on how the tables should be made available to the public. By this report the National Research Council is transmitting the results of the review of the working group's draft report that the subcommittee conducted in fulfillment of these tasks.

The original tables (NIH, 1985) were mandated under Public Law 97-414 (the "Orphan Drug Act") and were intended to constitute a means to estimate the likelihood that a person who has or had any of several radiation-related cancers developed cancer as a result of exposure to ionizing radiation from the nuclear-weapons tests in Nevada. The mandate included provision for periodic updating of the tables. The motivation for their current revision reflects the availability of new data (especially on cancer incidence), of new methods of analysis, and of the need for a more thorough treatment of uncertainties than was attempted in the original tables.

At the meeting on May 16-17, 2000, the subcommittee heard presentations by members of the working group charged with the revision, specifically, Charles Land and Ethel Gilbert, of the National Cancer Institute, and Owen Hoffman, Iulian Apostoaei, and Brian Thomas of SENES Oak Ridge, Inc. The presentations dealt with the strategy adopted in the revision of the tables, the demonstration of the Interactive Radio-Epidemiological Program (IREP) developed for the computation of assigned share (AS), and specific portions of the program and the default values.

2. SUMMARY OF THE SUBCOMMITTEE'S REPORT

The revised radioepidemiological tables provide an update of the probabilities of causation based on new epidemiologic data and statistical models, and they represent a comprehensive attempt to model the uncertainty in estimating radiation risks. The working group has used a systematic approach to analyze radiation effects identified in studies of the Japanese survivors of atomic bombs; so risk estimates for the various tumor sites should be comparable. It has also provided broad coverage of tumor sites, so its draft report and the accompanying computer program are widely applicable.

The working group used information on uncertainty in its models when it was available and made sensible choices of ranges of uncertainty when direct information was not obtainable. It then applied a Monte Carlo analysis to model the uncertainty inherent in the risk estimates. Their Monte Carlo approach allowed flexibility in the modeling of uncertainties, rather than constraining the model to fit specific distributions.

The provision of a computer program incorporating the risk and uncertainty models allows users to model the circumstances of their exposure and to derive an overall estimate of radiation-associated AS. For all those steps, the working group is to be commended.

3. CRITIQUE

Utility of the Data Sources

Incidence data from the study of the Japanese survivors of atomic bombs were used to define risk coefficients per unit dose of radiation for various cancer types. The strength of these data include: the exposed group is large and duration of follow-up is long, there are organ-specific dose estimates for individuals, there was a wide range of doses, there is appreciable information in the low-dose range (most of the subjects received doses of less than 10 cGy), all organs and tissues were irradiated, people of all ages at the time of exposure were included in the study, outcomes were not biased by medical conditions that would have prompted irradiation, and medical follow-up was of high quality. The Japanese study is not without its limitations, however: estimates of the denominator for the tumor-registry data are imprecise (only approximate estimates of the size and composition of the atomic-bomb population still residing in the catchment area of the Hiroshima-Nagasaki tumor registries are known), cancer-incidence data are more subject to effects introduced by the manner in which the surveillance is conducted than cancer-mortality data, dose uncertainty might affect the risk estimates in unknown ways and degree, the magnitude of the neutron component of the exposures is uncertain, and there was no dose fractionation or dose protraction, as there would be in typical occupational exposures. Those caveats notwithstanding, the subcommittee views the data resulting from the studies of the Japanese survivors of atomic bombs as an acceptable basis for estimating risk now. In the future, however, a broader-based radiation risk assessment should be used for tumor sites for which there are other high-quality sources of data available for estimating risk. The inclusion of data on exposed Western populations and groups with fractionated or protracted exposures will lessen reliance on the "transport" and the dose and dose-rate effectiveness factor (DDREF).

The Working Group's report includes all cancer sites addressed in the 1985 Radioepidemiological Tables except bone cancer associated with injection of ^{224}Ra and lung cancer associated with inhalation of radon decay products. No explanation is provided for either

of these exclusions, except to note that the present report is only "an interim update" in light of the Biological Effects of Ionizing Radiation (*BEIR VII*, phase 2) report expected in a few years, which will provide a much more thorough analysis of radiation risks but not for the two cancer risks exluded. Certainly, the incorporation of radon exposures would require special treatment based on completely different data sources from the atomic-bomb survivor cohort, namely, the extensive reanalysis of 11 cohorts of underground miners and case-control studies of residential radon performed by the BEIR VI Committee (NRC, 1999). Although, it can be anticipated that the addition of a module for computing ASs for radon-exposed lung cancers will be part of the next update of IREP, it is unfortunate that it was not included in the present report, inasmuch as there is a particularly timely need for it. The BEIR VI report provides a well-established model for computing ASs and their uncertainties without having to undertake any new data analyses. In response to the recommendation by the President's Advisory Committee on Human Radiation Experiments (ACHRE) that compensation policy for the Colorado Plateau uranium miners be re-examined, the Department of Justice (DOJ) convened an expert panel in 1996 to prepare a new set of radioepidemiological tables (DOJ, 1996) for use in developing an amendment to the Radiation Exposure Compensation Act (RECA). As noted by ACHRE, the scientific basis of the RECA has advanced considerably since the act was passed, and a more appropriate basis for compensation is badly needed.

Data Sources for Estimates of Uncertainties

The working group based its evaluation of uncertainty in radiation risk coefficients and models primarily on analyses of data that have been conducted with the studies of the Japanese survivors of atomic bombs. For specific cancer types the working group evaluated uncertainty distributions by sex, age-at-exposure, time-after-exposure, and age-at-observation. For thyroid cancer, the working group's uncertainty estimates were based on an analysis of pooled data from several studies (Ron et al., 1995).

The uncertainties in random errors in dosimetry were based on the main analyses of the dose-specific risk factor in the atomic-bomb study. The source of data used to model uncertainties in the relative biological effectiveness (RBE) of neutrons or to model systematic bias in the gamma and neutron dose estimates is unclear; one would have to review National Council on Radiation Protection and Measurements (NCRP) Report 126 (NCRP 1997) to determine this. It is recommended that the working group elaborate on these uncertainties in its report.

Estimation of the DDREF for low-LET radiation rests, in part, on data summaries and judgments by the International Commission on Radiological Protection (ICRP), NCRP, and the Environmental Protection Agency (EPA), but uncertainty distributions and modeling of the DDREF were apparently based on the working group's own judgment. That seems reasonable and preferable to the use of a single DDREF value. However, the working group should state how it derived the uncertainty distributions for the DDREF.

Estimates and uncertainties of the RBE values for high-LET radiation were based on the most comprehensive and authoritative summaries available. The large uncertainty factors used for the RBE values are appropriate, given the diverse results found in experimental studies.

The transfer of radiation risks from the Japanese population to the US population was handled by Monte Carlo simulation to determine the average of the risks derived with additive and multiplicative models. The use of a trapezoidal distribution appears to be a defensible way to do this. The transfer used the atomic-bomb risk coefficients and the comparative baseline rates of cancers in the United States [Surveillance, Epidemiology, and End Results (SEER Registry)] and the atomic-bomb-unexposed group.

Uncertainty regarding the lung-cancer risk posed the by interaction of smoking and radiation was modeled in the same manner as in the 1985 radioepidemiological tables report, but the population distribution of smoking habits was updated to reflect a 1993 CDC national survey. Because of several published analyses of the form of the interaction, the working group chose a distribution of uncertainties that weighted the result toward a multiplicative interaction. The data used and the choice of an uncertainty distribution are reasonable.

The working group decided not to try to account for uncertainties in genetic susceptibility to radiation carcinogenesis. That decision was based on the most comprehensive and authoritative monograph to date (ICRP, 1998), which indicated that present knowledge does not indicate that interactions between radiation exposure and genetic sensitivity will have a substantial impact on population risk estimates. The subcommittee notes that even if that is true at the population level, it might not be true at the level of the individuals for whom claims are being adjudicated, inasmuch as at least a few genetic conditions are known to be associated with an increase in radiosensitivity and more conditions might be identified. The working group should consider whether to build a special provision into its model to allow for such conditions.

In summary, the subcommittee believes that the working group has for the most part done an excellent job of selecting data sources on which to base its model of AS. However, there is a need to clarify its sources of information on uncertainties with regard to RBE, DDREF, and the "miscellaneous" category. More thought should also be given to the inclusion of a systematic risk factor in the model for people with known predisposition to genetic radiosensitivity and the uncertainties inherent in such a factor.

Assumptions Concerning Radiologic Effects

The working group's analysis is based on the use of models of excess relative-risk (ERR). With the inclusion of appropriate modifiers of excess risk (such as, time-since-exposure, age-at-exposure, and attained age), these models can be used to describe the Japanese and other radiation-epidemiology datasets. Other models, such as models of excess absolute-risk (EAR), can also be considered but might not lead to different conclusions about AS. In fact, if these modifiers of risk are appropriately included in the modeling, either ERR or EAR models should function equally well for the purpose of producing AS tables.

The working group based its assumptions about the appropriate models of radiation risk primarily on previous analyses of the atomic-bomb data by the Radiation Effects Research Foundation (RERF) investigators. The analyses of data for solid cancers, taken together or at a number of specific or grouped sites, support a linear dose-response association and do not indicate that fit would be improved by the addition of a dose-squared term. The assumption of linearity seems reasonable, therefore, and rests on the best available information. The atomic-bomb study is also the best source of data on the shape of the dose-response curve for leukemia; in this case, it supports a linear-quadratic model.

Most treatments of RBE and DDREF by radioepidemiologists and radiobiologists have assumed that their values are constant. The working group has been innovative in introducing uncertainty factors for these values, and this has advanced the discussion.

The NRC oversight committee (1984) noted that the treatment of extended exposures assumed that each increment of exposure contributes additively to total risk (although possibly with different weights related to the DDREF). That assumption is conventional, but seldom acknowledged, in radiation epidemiology. A variety of experimental and epidemiologic data on

low-LET radiation indicate that the risk posed by highly fractionated or protracted exposures is not greater than, and even tends to be less than, that posed by an acute exposure of the same total magnitude. The subcommittee therefore agrees that the assumption of additivity is reasonable and that there is no need to build into the model a potentiation of effects by serial exposures. However, the working group should provide a fuller justification in its report for assuming multiple or protracted exposures are additive in their effects and the impact on AS estimates if this assumption is incorrect.

A brief summary of what is known about additive or interactive effects of exposure to radiation and other toxic agents (besides cigarette smoke) would also be informative for the broader scientific and user communities. In particular, users might wonder whether a person's radiation exposure potentiated the effects of other toxic agents to which he or she was exposed.

Modeling and Choice of Parameters

The working group chose to base its AS calculations on separate analyses of the Japanese atomic-bomb survivor data on each of 33 sites of cancer. That is justified by the fact that each cancer type is a distinct disease, with different biologic processes that lead to potentially different degrees of radiosensitivity or modification by age, sex, latency, and other factors. The possible heterogeneity among cancer sites must be weighed against the smaller number of cancers available for analysis, as subdivision of tumor types becomes increasingly fine with a consequent increase in uncertainty in parameter values and lower power to effects of modifying factors. At the same time, the upper-bound confidence limits on calculated probability of causations (PCs) might become so large that no cases could be excluded as radiogenic, no matter how low the dose. The subcommittee believes that for the major cancer sites, the working group has struck a sensible balance—allowing for some differences between cancer sites but not subdividing the data more finely than is warranted. In the case of some of the rarer sites,

however, estimates for groups of sites might be more reliable, barring convincing evidence that the sites really are different.

4. TREATMENT OF ACUTE AND PROTRACTED (CHRONIC) EXPOSURES

The level of detail incorporated in the working group's report and in the model pertaining to acute, fractionated, and protracted (chronic) exposures seems disproportionate to the amount of information in the average occupational record. Few records contain more than weekly exposure estimates, and most have only monthly or quarterly measurements or yearly summaries. It therefore seems unlikely that the acute-chronic choice in the IREP can be useful. Instead, the officials responsible for adjudicating compensation claims might routinely assume that the exposure aggregated over the smallest unit of time available (such as a quarter-year) was received as a single acute dose to provide a liberal estimate of risk. The working group's report should discuss the situations with limited information on exposure and provide recommendations on how to use the program in such cases.

Many users might not understand the rationale for or implications of using the acute-chronic option, and a clear explanation should be provided that is appropriate for the types of exposure information likely to be available.

5. ASSESSMENT OF TIME-SINCE-EXPOSURE AS A MODIFIER OF RISK

With respect to modification of risk by time-since-exposure (TSE), it is unclear why the working group's analyses were limited to linear trends in TSE (except for leukemia). There are precedents for nonlinear trends: that between radon and lung cancer and that between external radiation and thyroid cancer. In the latter case, there is evidence of a nonlinear TSE effect in which the risk first increases then decreases. Nonlinear TSE trends are also compatible with a multistage model wherein an intermediate stage is affected by the exposure.

6. APPLICABILITY OF ASSIGNED SHARE CALCULATIONS TO MINORITY GROUPS

The working group's draft report gives little consideration to the appropriateness of AS calculations to minority groups, nor does it provide an alternative for cases in which the baseline rates of particular cancers differ appreciably between specific minority groups and the average population. Although data about ethnic differences in population rates may be available, there are generally few or no data on differences in their radiation risks. In principle, the problem is analogous to the transport of ERR from the Japanese to the US population. US ethnic groups clearly differ in some cancer rates; for example, Hispanics have lower rates of breast cancer, Hispanics and African-Americans have lower rates of thyroid cancer, and African-Americans have higher rates of prostatic cancer. Because of uncertainty as to whether a multiplicative or additive model is more fitting for the transport of risk, an "automatic" transport of risk via the ERR model might be inappropriate. The working group should consider what to do about the transport of risk among ethnic groups; it might have to revise the IREP to allow the transport to be taken into account.

7. ESTIMATION OF ASSIGNED SHARE FOR NONMELANOMA SKIN CANCER

The subcommittee recommends that the working group develop AS estimates for nonmelanoma skin cancer (NMSC), because NMSC commonly requires adjudication by compensation boards and there is clear evidence that radiation can cause skin cancer. It should be possible to develop a pooled risk estimate from the several major studies of radiation and NMSC and to estimate from them the importance of appropriate features or risk modifiers, such as age-at-exposure, race, and shape of the dose-response curve (Ron et al., 1991; 1998; Shore et al., 1984). If so, the working group should take into account the likelihood that the dose-response relation is nonlinear with little evidence of an effect in the low-dose range of interest in these radioepidemiological tables.

Although baseline rates of NMSC in the United States are not well characterized for recent years, it should be possible to estimate the US rates in Caucasians on the basis of earlier rates obtained by Scotto and others (Scotto, 1974, 1983) in the SEER Registry study, with adjustment to reflect temporal trends in NMSC rates as reported by them and others (Fears and Scotto, 1982; Glass and Hoover, 1989; Karagas et al., 1999; Miller and Weinstock, 1994). The added uncertainty associated with the estimated US baseline rates might be incorporated as part of the transport uncertainty.

8. TREATMENT OF UNCERTAINTY

Monte Carlo Simulation

In developing its computer program (IREP) to calculate the probabilities of causation, the working group used Monte Carlo simulation to model uncertainties in the estimates. To help readers appreciate this change in method, it would be useful for the report to include a comparison of the methods used to account for the uncertainties in the 1985 tables and in IREP. This comparison should include assumptions of methods used, data needs, and improvements achieved by the new method. This comparison should also include some discussion of where the two sets of tables differ most.

In the original tables, the authors identified a series of parameters to which they assigned uncertainty distributions: baseline values, influence of age-at-exposure, time-since-exposure, ratio of linear coefficients in the linear and linear-quadratic dose-response models, latent period, and risk coefficients. They assumed that each uncertainty distribution was lognormal and specified a geometric standard deviation (GSD). To propagate the individual uncertainties and calculate the GSD for the overall uncertainty distribution, S, they combined the individual GSDs, S_i, into an overall GSD by using this equation:

$$(\ln (S))^2 = (\ln (S_1))^2 + \ldots + (\ln (S_k))^2$$

That resulted in a lognormal distribution of uncertainty about the estimated probability of causation. This method of combining individual uncertainties has limitations: the distributions are assumed to be lognormal and the appropriateness of this assumption is uncertain, the distributions can be combined only through addition of the logarithms of the GSDs, and the GSDs have to be estimated for each parameter.

The working group should provide a summary of its approach pointing out the advantages and the limitations of the Monte Carlo method. For example, it might note that Monte Carlo simulations offer greater flexibility in modeling the uncertainty distribution of estimates of a particular quantity. It might also note that the method requires that each parameter estimate be assigned a distribution. The distributions can be specified as theoretical functions or they can be specified empirically. Then, for each run of a large set of simulations—say, 10,000—a parameter set is developed by selecting a value for each parameter from its specified distribution. The sampling strategy can be random or structured so as to emphasize particular parts of the parameter hyperspace (for example, by Latin hypercube sampling). Once selected, the parameter values are combined by using a previously specified equation into an overall estimate of the probability of causation. Two advantages of this method are that the user can specify any distribution shape for each uncertainty distribution and that the combination of uncertainties is not limited to additive and log-additive (ERR) models. Two limitations are that one has to estimate the shape and variance of the uncertainty distribution for each parameter and that one has to run enough simulations to be confident in the stability of the estimates, particularly in the tails of the distribution. If all the distributions needed for a Monte Carlo stimulation are specified as lognormal and they are combined in a multiplicative model (the sum of the logarithms), the results should be essentially identical with the results of the old method. It is important to note that in both instances the calculations include only the uncertainty distributions specifically noted. As stated in both the 1985 report and 2000 draft report, many other aspects of uncertainty are not included and are likely to give rise to additional uncertainty.

Both the method used by the working group and the one suggested above assume that all parameter uncertainty distributions are independent (uncorrelated). If parameter estimates were positively correlated, failure to model their dependence would result in underestimates of the uncertainity. One difference between this approach and that used by the EPA, which it would be useful to point out, is how the slope-factor uncertainty is modeled. EPA uses the 95% upper confidence limit of the potency-slope factor as a fixed-point estimate; IREP uses a regression-

based approach to estimate the parameter and its uncertainty distribution. Another difference is that EPA sometimes uses two-dimensional Monte Carlo analysis, which separates effects of variation from those of uncertainty. IREP does not make that distinction. Clarifying those differences and explaining their consequences would be informative for users. Although the specification and use of GSDs to describe the uncertainty of specific parameters and the combination of these values algebraically are fairly transparent, the use of IREP is opaque. For the general public, a clear discussion of how it works, with limitations and assumptions, would be useful. It might also be worth while to point out the slope-factor uncertainty.

Finally, the working group conducted inadequate sensitivity analyses to show some of the effects of the changes in the data and methods quantitatively. Some of the AS values estimated with the IREP will be lower than those listed in the older tables, so it will be important to explain clearly which changes in data or modeling led to the lower estimates. In short, the impact of each change in how AS has been modeled must be described, including the uncertainty modeling.

Residual Uncertainties and Use of a Scale Factor

Following the method set forth in NCRP Report 126 (NCRP, 1997), the working group has included a "catch-all" factor for additional, nonspecific sources of uncertainty. Its report notes that a precedent for this was set in the 1985 tables. The additional, nonspecific sources are noted in the text, but the subcommittee does not see that they were included in any of the calculations (except for smoking) and this should be made clear.

The subcommittee is uncomfortable with the inclusion of an uncertainty distribution for unknown or unidentified factors and with the rationale for it. On the one hand, it can be argued that the use of the 99th percentile limit in the AS in effect already allows for this and that an

additional, miscellaneous factor might not be necessary. On the other hand, its inclusion provides assurance that the calculation favors approval of possibly meritorious claims by affected people.

We recognize that the IREP formulation is not exhaustive in its inclusion of factors that contribute uncertainty to the estimate of overall risk. However, we believe that it is inappropriate to include an uncertainty distribution for unspecified factors and that it is not possible to specify a distribution for such factors. In place of the current general scale factor, we recommend an option to enable users to include a factor in addition to those explicitly stated, provided that they specify a name and a distribution. To implement that option, the general scale factor should be renamed "additional uncertainty factor", its default GSD should be set to 1.0 so that it will have no effect unless altered by the user, and a user who wishes to include this factor, should first have to specify a name for the uncertainty distribution (that is, identify specifically what variation the factor represents) and then specify the GSD. It is important that the strongest possible justification is set forth for the choice of the GSD when this factor is used.

To summarize, the Radioepidemiological Tables Working Group is to be commended for its careful consideration of uncertainties in the estimates of AS. These uncertainties range from statistical sampling errors in the estimated relative-risk parameters that can be directly computed from the data to a variety of potential biases and sources of uncertainty (such as measurement error, dose-rate effects, and risk-transport problems) where some data exist to suggest a reasonable range of values to a miscellaneous category of other uncertainties for which it is impossible to justify any particular choice of values. The subcommittee generally endorses the methods that have been used to address the first few sources of uncertainty and the specific distributional parameters that have been adopted.

9. HOW SHOULD THE RADIOEPIDEMIOLOGICAL TABLES BE MADE AVAILABLE TO THE PUBLIC?

a) Evaluation of the Interactive Radio-Epidemiological Program:

The working group began with the assumption that revision would result in a series of tables similar in style to the original ones. As work progressed, however, it became apparent that an alternative existed—to develop an interactive computer program that would make it easier for a potential user to calculate the risk to an individual, assuming the user has sufficient information at hand. The working group chose this alternative, and the result is an application for the personal computer—the Interactive Radio-Epidemiological Program (IREP)—that uses a visual programming tool, known as ANALYTICA, with an accompanying user's guide.

The subcommittee notes that consideration of the intended users is basic in any review of a software system. A system intended for a small, highly trained group would have design objectives that differ in important ways from those of a system intended for the general public. Ease of use, for example, is generally far more important for the latter than for the former. Moreover, systems to support public-policy decisions must meet criteria that do not apply to other systems, regardless of the audience. In addition to balancing design criteria, such as ease of use and clarity of presentation, systems that support public-policy decisions must meet the following three criteria:

- *Accessibility* To ensure public confidence in the decision process, the system must be available to all stakeholders affected by decisions that depend on its use.

- *Transparency* All underlying assumptions must be clearly presented to the user (and captured in the system's outputs).
- *Flexibility* If a system incorporates assumptions that are not formalized in legislative or regulatory policy or that do not represent an overwhelming scientific or policy consensus, they must be subject to modification by the user.

According to information provided by the design team, IREP is intended for use primarily by a comparatively small community of relatively sophisticated users. However, the design team has given consideration to the system's status as a policy tool and has assumed that it will be broadly available to the public. The design has attempted to address this assumption. Overall, the working group has had mixed success in meeting these goals, which might reflect resource limitations. Specific suggestions for improving the user interface are noted in the appendix to the working group's draft report.

Accessibility:

Using IREP requires downloading of a "browser" version of ANALYTICA from a Web site (http://www.lumina.com). Presumably, if the working group distributes the ANALYTICA-based version of this software, it will make arrangements to "bundle" the required browser software with the application.

Development of a Web-based application was discussed by the working group at the first meeting of the subcommittee. The desirability of such an approach will be dictated by the expected user base, which in turn reflects the need of the Department of Veterans Affairs (VA) and other users for this tool to operate openly. In particular, if applicants for benefits will need access to the program, more work will be necessary to ensure not only access, but also transparency and user friendliness.

One unnecessary restraint on system access is how identification information and other personal information are collected by the system. This may be of concern to potential users, particularly if a Web-based implementation is chosen. For example, there is no need to collect the name of the person being evaluated, and this field should be made optional. More important is the specification of birth year and year of diagnosis as fundamental data items. The important variables to collect are age at each exposure and age at diagnosis of each cancer. There is no need to collect data on calendar years for this, although it offers convenience for data entry; this convenience needs to be balanced against a large perceived threat to privacy, particularly if someone is using a Web site and distrusts the government. An option for different ways to enter time information would address this concern.

Transparency:

The transparency of IREP could be considerably improved. The "Help" function, for example, calls ANALYTICA help, rather than model help. The latter can be accessed by a series of context-specific buttons, but it is not easy to move among topics. A standard Windows help file would be better. It might be possible to let users have a choice of help files in the help window.

More important, the program (IREP) does not adequately convey the nature of the problem that it is designed to address, nor does it distinguish the analysis that it provides from other kinds of analysis to prevent misunderstanding by inexperienced users. At a gross level, the program needs to warn users that the information it provides cannot be used in the prediction of cancer risk. At a more refined level, it should clearly explain the underlying assumptions of the analysis and some of their consequences. Section 10 on "Broader Issues" identifies some places where

less-experienced users will need carefully prepared explanatory material that is accessible directly within the IREP.

The system presents its report on the contribution of various factors in extrapolation to uncertainty only in relative terms, although it calculates the absolute magnitude of the uncertainty. It might be helpful to offer users a choice of how to present information on each component's contribution to total uncertainty in the prediction of AS, that is, to supplement the pie-chart analysis with a stacked-bar presentation of the data.

Flexibility:

A variety of options are available to permit personalization of the computations, including personal information (age, sex, and the like), exposure (number, years, organ dose, dose rate, and exposure type), and type of cancer. However, because IREP's uncertainty-analysis modules are the driving feature of the decisions made by this system, it is important for users to know that the assumptions made in assessing uncertainty fall into three categories: locked by policy (and whose policy has locked it), current state of the science (and what peers have vouched for it), and modifiable by the user.

The last category seems to be relatively rare (particularly if the distributed form of the software will be analogous in operation to ANALYTICA in the browser mode). The development team has clearly gone to great lengths to make underlying assumptions accessible to users (including the mathematical description of how assumptions are operationalized), but these choices cannot be user-modified. The inability of users to modify critical system assumptions calls for greater attention to documenting the policy and scientific foundations of the assumptions.

Among the key system assumptions not editable by users in the ANALYTICA browser and potentially in need of additional justification or an option for user modification are these:

- ERR/Sv cumulative probability tables for organ systems (starting data; *ERR/Sv data*).
- Rank-order correlation for multiple exposures (*Correlated ERR/Sv*).
- Adjustments for latency (*ERR/Sv latency*).
- Truncation (at zero; *ERR/Sv truncated*).
- Distribution form and parameters for errors in dosimetry (see page 32 of working group's draft report).
- Gamma and neutron bias and neutron uncertainty (systematic errors in dosimetry; *Bsed*).

Users can modify the sampling approaches used in the Monte Carlo analysis. This option could have an important and possibly self-serving impact on the results that are generated. If this is unintentional, the working group must disable the relevant selection and explain why the particular option (median Latin hypercube sampling with "minimal standard" randomization) is preferable to alternative methods commonly used in Monte Carlo analysis or provide users with a clear explanation of the rationale for selecting among the available options and the consequences of selections for the resulting prediction at different Monte Carlo sample sizes.

A similar issue concerns the selection of sample sizes. The default is set at 1,000, which does not yield particularly stable predictions of the 99th percentile AS value in repeated runs for

at least some cancer sites (a 10-fold increase in sample size yielded increased stability, albeit at a substantial cost in processing time). The working group needs to document the results of a parametric examination of alternative default options as part of its internal testing of the software.

The design team deserves considerable praise for its efforts, not only with regard to its specific mandate, but also with regard to a broader understanding of the policy context of that mandate. The interactive software offers many advantages over the tables that it supplements, and there has clearly been careful thought about the implementation of the specified analysis. However, considerable development work is warranted before this product will be suitable for any but highly specialized audiences.

b) Other Ethical and Communication Issues:

Informing the public about the IREP will be difficult but necessary. A number of communication issues present themselves, including language and conceptual problems. One language problem involves explaining differences among risk, PC, and AS. For example, a member of the public might try to run the PC calculation for a cancer that has not yet occurred and misinterpret the resulting value as the probability that it will occur in the future. Although using the term *PC* might provide serious technical problems in the IREP, PC might be more understandable to laypersons than AS because many people are familiar with the words *probability* and *causation* in the context of health and environmental risks. Explaining AS, a concept unfamiliar to many, will be more difficult. That is not to suggest that AS not be used as the prime term in the IREP, but it is worth recognizing that AS is not well understood by most laypersons. When the IREP information is communicated to the public, attention should be paid to explaining AS in some detail—not just defining it.

A second language and conceptual problem is the difficulty of explaining anything related to probability or statistics to laypersons. Helping them to understand probability often requires use of analogies (such as, weather forecasting and dice throwing). Getting people to understand Monte Carlo simulations will take more effort. Considerable care will be needed to translate statistical concepts that are important for public understanding of the IREP. This problem is made more acute by the fact that even audiences familiar with probability and statistics (such as risk assessors) must devote considerable effort to familiarize themselves with the assumptions on which AS is based and with the resulting choice of statistical methods.

An initial comparison of the IREP model with the 1985 tables conducted at the VA suggests that the new model will lead to differences in compensation. It appears that using the IREP model will make it somewhat less likely for people to be compensated than in the past. If using the model denies more people compensation, this situation must be acknowledged in a public summary, and the factors causing the increased claim denials should be explained. If care is not taken, using the IREP might create serious risk communication problems for the VA, with the agency being accused of applying it only to save money and not to assist veterans.

The National Cancer Institute (NCI) has suggested that the program (IREP) and the public summary be made available on its Web site. The subcommittee endorses NCI's efforts to make both more accessible to potential users. However, putting the program (IREP) on a Web site so that lay people can use it presents a number of communication questions that must be evaluated in depth. First, directions on how to use the program will have to be readily understandable. Second, the various radiologic and statistical concepts involved must be carefully explained; computer graphics and animation might be helpful, but expensive. Third, and most important, it will be essential to provide context for and explanations about how to interpret the final numbers coming out of the model and what they mean for an individual, from both health and compensation perspectives.

A Web site that includes technical information and models will not automatically be an effective communication tool. Careful thought and planning will be essential in the design and monitoring of the use of the Web site to ensure its effectiveness in disseminating information about the revised tables. Questions to consider about the Web site include these:

- Will the Web site include means to measure its effectiveness and the applicability of the model developed by the working group?
- Will measures of the effectiveness of the Web site and the model be built into the site?
- How user-friendly can this program be with its complicated information?
- Should there be other parts to the Web site, including a chat room or a frequently-asked-questions section?
- Will there be a way for a user to get e-mail information from a VA representative about problems in using the site or about interpreting the information in the model regarding his or her case? Would such a system add to the present workload of the VA?
- Who will maintain and update the Web site as needed?
- Consideration should also be given to possible Web sites in languages other than English, notably Spanish.

In addition to the Web site, however, the subcommittee recommends that a printed public summary be available to potential users and family members who do not have ready access to computers and the Internet. The question of computer accessibility also comes up for members of lower economic and minority groups. To get information to those groups, it will be important to have a printed public summary–perhaps in brochure or newsletter format–that is widely distributed to ensure that everyone interested in VA compensation issues gets a copy.

Any printed version of a public summary should include well-designed graphics to help to explain the complicated concepts involved in the IREP. It also should include many of the graphic pages in the current user's guide that show how the model works. However, the language in the guide, which is for a technical audience, will not work well for the general public.

Finally, but no less important, the subcommittee notes that ethical and communication issues transcend the use of a Web site or printed material. The paramount ones are these:

- How should the issue of privacy of medical information be addressed?
- How will people find out about the revised tables?

10. FUTURE REVISIONS AND BROADER ISSUES

Future Revisions:

The present set of analyses of radiation data for deriving AS estimates are based almost exclusively on the Japanese atomic-bomb data. In the future, it would be valuable to use a broader range of data (for example, those to be presented in the impending reports from the United Nations Scientific Committee on the Effects of Atomic Radiation and the Biological Effects of Ionizing Radiation (BEIR VII, phase 2)), either to analyze conjointly or to use in evaluating the consistency and uncertainty of the results. In addition to helping to ensure the validity of the radiation-risk assessment, this would lessen the uncertainties.

The subcommittee further suggests that future analyses explore an alternative approach based on hierarchic random-effects models (Witte et al., 1994; Greenland 1992, 1993, 1997). In this approach, site-specific cancers might be grouped a priori in some hierarchic fashion (for example, according to levels of the International Classification of Diseases). Each branch of the hierarchy would be associated with a variance component for slopes of dose-response relationship and perhaps for the magnitude of modifying effects of age, sex, latency, and so on. These variance components would not be specified in advance, but would be estimated from the data. The slope estimates (and modifying effects) for any given cancer type would then be weighted averages of the direct estimates for the specific types and for the aggregate estimates at the higher level(s) of the hierarchy, each weighted by corresponding variances. Thus, for groups of cancers showing little difference in their slope estimates or modifiers, the smoothed estimates would be dominated by the overall model for the larger group, and estimates for cancers for which there is compelling evidence of substantial variation would be dominated by the subgroup estimate.

A somewhat related approach known as Bayes model averaging (Madigan and Raftery, 1994; Carlin and Chib, 1995; Carlin and Louis, 1996) might be considered to address questions

of uncertainty about the appropriate model form. Rather than rely on a priori or data-driven decisions about what effects to include in the model (for example, whether to add a quadratic dose-response term or age and latency modifiers), one would fit a broad suite of alternative models and report a weighted average of their predictions—weighted by their respective posterior probabilities. This approach has the appealing feature of providing confidence limits that reflect the uncertainty about true model form. However, it should be noted that although these alternative analyses will reduce the arbitrariness in the grouping of cancers to some degree, they cannot eliminate it.

Broader Issues:

The subcommittee was not specifically charged with an evaluation of the various compensation schemes currently in use, but some consideration of the latter is, in our view essential, for the assessment of the proposed revision of the radioepidemiological tables. This follows from the fact that a major purpose of the tables is to provide a means for evaluating the merit of specific claims for compensation, and the utility of the tables therefore has to be seen in the context of the compensation systems that they are intended to serve. Different policy decisions have different implications for compensation, and these differences can impinge on the utility of the tables. Accordingly, in the paragraphs that follow, we examine, albeit briefly, some of the schemes that are in use or could be proposed to adjudicate claims for compensation and to settle tort litigation. Our focus, however, is on improving administrative uses, such as those pursued by the VA and the DOJ, and not judicial uses. Although the subcommittee believes that the principles might be the same and our recommendations might be equally applicable to both kinds of use, the legal profession was not represented on the subcommittee, and civil litigation cases seldom turn on the value of the PC estimate alone.

Usefulness of Probability of Causation:

The 1984 National Research Council Oversight Committee noted that the so-called probability of causation was strictly speaking not a probability, but rather an estimate of the *proportion* of cancers that were caused by exposure in a large (hypothetical) group of similarly exposed cases—an estimate that was then *assigned* to all members of the group. Therefore, the committee recommended the use of the term assigned share for this quantity, and this recommendation was adopted by the working group in the current revision. One of the reasons, the National Research Council Oversight Committee chose assigned share over probability of causation was the possibility of a hazard ratio less than one. However, in the present instance, the working group used only models for which the hazard rate for the exposed group is always greater than the hazard rate for the unexposed group. That ensures a positive numerator in the standard PC formula and guarantees that the expression is a probability. Given that fact and that the literature on probabilistic causality (see Pearl, 2000 for a review) generally uses probability of causation or a probability of a cause, a term traceable to Laplace (1774), we have used probability of causation and assigned share as essentially synonymous in this context. Pearl (2000) discusses the conditions for identification of necessary and sufficient causes and illustrates the concepts with an example of the effect of radiation on leukemia. But the subcommittee wishes to explore some questions related to the concepts as statements of causality somewhat more deeply.

Since the publication of the original radioepidemiological tables, a growing statistical literature has called into question the validity of not only the PC, but even the AS concept Greenland, 1999; Beyea and Greenland, 1999; Greenland, In press). For example, Robins and Greenland (1989) have derived bounds for population averages of PC for heterogeneous populations and studied the effect of independent and dependent censoring on these bounds. It can be claimed, however, that population averages are not of interest in the compensation of a particular individual (Groer, 1985). Robins and Greenland (1989) have also argued that in the

presence of some kinds of individual variability, a person's PC cannot be estimated without recourse to additional assumptions that are inherently unverifiable. They describe examples of hypothetical models in which *every* case's date of death was advanced by exposure (perhaps only by a small amount), although the ERR (and the PC) could be arbitrarily small. They interpret that situation as implying that exposure "contributed to" disease in 100% of the cases and hence that some compensation would be deserved, but none would qualify under a PC (or AS) criterion that required at least a 50% probability. However, if a set of individuals, exchangeable with this particular individual, can be identified, the parameters of a suitable dose-response model and the PC can be estimated under the assumptions specified by Robins and Greenland (1989). It should be noted, nonetheless, that parameter estimation in the presence of competing risks usually assumes independence of the event of interest and the competing risks. If that assumption is dropped, the estimates of the model parameters and of the PC will change. The form of the dependence is not known, so one can only establish bounds for the parameter estimates. These bounds correspond to extreme forms of dependence.

Robins and Greenland (1989) show further that the AS computed for a group of individuals will not, in general, be a valid estimator even of the *mean* of the individuals' true PC and will usually be an underestimate of the true *mean* PC. Again, unverifiable assumptions would have to be invoked to allow such an interpretation of the AS as a mean of individual PCs; such assumptions would include the absence of individual variation in baseline risks, an assumption that is almost certainly false.

The subcommittee agrees with the Robins and Greenland's mathematical analysis but is somewhat skeptical about its practical significance. The magnitude of the bias in the AS depends on the extent of the population heterogeneity in baseline rates. Although this heterogeneity cannot be estimated from incidence or mortality data on independent individuals, family or repeated-events data can provide an idea of how large this variability could be. Data on Danish identical twins lead to an estimate of about a 7-fold range in multiplicative factors

("frailties") between 80% of individuals (Hougaard et al., 1992). Using this estimate, Thomas (In press) has described the magnitude of the potential bias and found that the overall correlation between individuals' PC that could be calculated if the true model and frailty values were known and the estimated AS is very high, even if in general the AS tends to underestimate the PC. The subcommittee is therefore persuaded that the AS approach still has some validity, at least for relative ranking of claimants.

A number of authors, including the 1984 National Research Council Oversight Committee, have pointed out various inequities that can arise in a compensation scheme that provides full payment to claimants with an estimated PC greater than 50% but none to those with PC less than 50%. At the simplest level, one can be disturbed by the profound difference between the treatments of two individuals with very similar claims. Add to that, the potentially large uncertainty in the PC estimates and the question arises whether such individual claims can be distinguished with any reliability. Furthermore, one can envisage situations in which hazardous exposures were so high that a substantial proportion of cancers in exposed individuals were indeed caused by the exposures but none would be entitled to compensation! An employer might thus avoid paying any compensation claims even though a substantial number of cases might have been caused by occupational exposure (although regulatory standards and the ALARA principle would tend to minimize the chances of this).

For such reasons as those, alternative compensation schemes have been proposed, most based on some kind of sliding scale in which the amount of compensation awarded depends on the magnitude of the estimated PC or on the uncertainty distribution of the PC estimates. For example, the 1984 National Research Council Oversight Committee suggested a scheme in which individuals with PCs greater than 50% would receive full compensation, those with less than 10% would receive none (to discourage "frivolous" claims), and compensation would be linearly scaled by PC in the range between 10% and 50%. Such a compensation scheme was

implemented by British Nuclear Fuels Ltd and the UK Atomic Energy Agency even before the 1984 NIH report (Thomas and others, 1991).

Robins and Greenland (1991) have argued that compensation schemes that pay in proportion to PC are neither "robust" to model misspecification nor "economically rational". In this context, a payment scheme is "robust" if the total amount paid to individuals *actually harmed by exposure* is the same under the two models, and "economically rational" if the total amount paid to *all* workers is the same. Those terms are intended to imply that the total amounts paid to individuals under an erroneously specified model will be equal to the total amounts that would have been paid under the correct model even if the payments to specific individuals were inequitably distributed under the erroneous model.

However, the same authors have considered other compensation schemes and contend that one based on the estimated loss of life expectancy (LLE) has some theoretical advantages. If payment is proportional to the estimated average loss of life, which can be estimated without invoking untestable assumptions, such a scheme is both robust and economically rational in the sense defined above and also provides a rationale for a gradient in compensation based upon the age of onset of the cancer (Robins and Greenland, 1991).

The choice of PC as the basis of compensation policy has specific implications. For example, suppose two populations have the same absolute excess risk of cancer due to radiation exposure but have different base line risks. In the high-baseline-risk population, the PC will be lower because it is more likely that the cancer was caused by factors other than radiation. However, the expected LLE due to radiation exposure in the total population (cases and survivors combined) will be about the same in the two populations if the disease is rare. In the latter case, the LLE is roughly proportional to the product of life expectancy in the general population and excess absolute risk, which we are assuming is the same in the two populations. Thus, the expected LLE due to radiation *among cases* would be higher in the low-risk population

because it equals the LLE in the total population divided by the total risk, which we are assuming is different between the two populations. A policy based on either the PC or the LLE would therefore correctly favor the low-risk population but would do so differently: a PC-based policy would reward a higher proportion of cases, but the size of the award would be the same for compensable cases in both populations; an LLE-based policy would reward all cases in both populations, but the average size of award per case would be greater in the low-risk population. Which is a more equitable solution is an important policy decision.

The subcommittee views those conclusions as worthy of more careful consideration by agencies responsible for establishing compensation and tort-litigation policy. We recognize, however, that the current policy is grounded on the notion of AS, and we do not wish to discredit the efforts of the working group by implying that its estimates are not useful as a basis for resolving such claims, even in the face of fundamental problems of interpretation. The subcommittee suggests that the appropriate branches of government consider whether compensation policy should be altered in favor of the use of proportional payment schemes, explicit consideration of uncertainties, and the use of criteria based on LLE rather than PC.

Role of Uncertainty in Compensation:

As previously stated, the working group is to be commended for its careful consideration of uncertainty in the estimates of AS. Questions remain, however, about how to handle the remaining components of uncertainty that cannot be quantified and about how they should be addressed in resolving compensation claims.

With regard to residual uncertainty, it should be noted that the problem has been lessened by extensive efforts to quantify many components of uncertainty and to reduce what remains. It would be helpful if the authors were more explicit in what types of uncertainty should be

included in this latter category so that readers would have a clearer basis for reaching their own decision about how large an allowance should be made for unquantifiable uncertainty. It is impossible to anticipate all possible sources of uncertainty, but they include differences between populations (for example, the US and Japanese populations) in the ERR coefficients that are being transported, misspecification of the form of fitted models, and uncontrolled confounding and other biases in epidemiologic studies. It should also be clarified that this category is intended to reflect uncertainty only in the estimated AS for the US population as a whole, not for individuals, in that the range of individual variation could be arbitrarily large and there is no basis for estimating just how large it could be.

As to compensation, some agencies, such as the VA, recognizing uncertainty, have used an upper confidence limit on AS (the 99th percentile in the VA) as a screening criterion to weed out claims that have little chance of being successful. In practice, however, few claims that satisfy the VA's screening criterion appear to have been eliminated in the adjudication process, presumably because little additional information can be brought to bear on the question of causality that was not already taken into account in the AS calculation—at least not information that offers a quantitative basis for shifting the estimate substantially. Hence, the upper 99% percentile is effectively the de facto compensation criterion.

That policy has the merit of liberality in that few claimants whose true PC (if it can be estimated) is greater than 50% will be denied compensation because their estimated PC is less than that value as a result of these types of uncertainty. However, this needs to be weighed against the expected number of payments to individuals with low "true PCs", which would be provided at the expense of all taxpayers or at the expense of other groups that are more deserving of government benefits. It is possible that the loss to such other groups is individually minuscule in comparison with the benefit to those who merit compensation but might be denied it under a more restrictive policy. Thus, this is a policy question that goes beyond the charge to the

subcommittee. However, we feel obliged to point out some technical anomalies that follow from the policy.

The subcommittee is disturbed by the implication that the less is known about a potential association involving low-level risks, the more likely a claimant is to be successful. Consider the following two scenarios. First, suppose that the relative risk (RR) for a particular exposure is estimated to be 1.8 with 95% confidence limits (1.7, 1.9), translating to an AS of 44% (CI 41%, 47%). Second, suppose that the RR is estimated at 1.1 with 95% confidence limits (0.22, 5.5), translating to an AS of 9% (CI 0, 82%), as might happen for a rare tumor type. Clearly, the first case provides stronger evidence of an association in the population (highly statistically significant), even though the AS for the group as a whole is less than 50%. In the second case, it is not clear that there is a causal connection in the population; the association is far from statistically significant, and the estimated AS is much lower. Nevertheless, under a policy that provides full compensation to those with upper 99% confidence limits on the AS of at least 50%, no members of the first group would obtain compensation, and all those of the second group would be successful. In short, the policy appears to reward lack of information and is counterproductive.

The subcommittee does believe, however, that uncertainty about age-at-exposure and time-since-exposure effects, has an important role to play in adjudicating compensation claims. We believe that the decision about potential causation must be addressed at the population level before the merits of an individual's claim are considered. That includes consideration of the level of statistical significance, the reliability of the epidemiologic database (freedom from bias, and so on), biologic plausibility and other criteria widely used to assess causality in epidemiologic associations. In large part, this has already been done by the working group and the various authoritative bodies on which its estimates are based.

With regard to the large number of cancer sites where no statistically significant dose-response relationship has been identified, the subcommittee notes that inclusion of these tumors constitutes a large departure from the 1985 tables, which considered only sites with a statistically significant dose-response relationship. We are sympathetic to the view that most tumors can be considered to be radiogenic to some degree; in many cases, the low background prevalence of these tumors in the Japanese population meant that the atomic-bomb study had low power to detect increased risk. Given that a number of tumor sites are being included in the Working Group's modeling for which there is not a persuasive association with ionizing radiation, the subcommittee believes that chronic lymphocytic leukemia (CLL) should be included as well. CLL could not be studied in the Japanese atomic bomb data because of the rarity of the disease there. Nevertheless, CLL is more common in Western populations and needs to be considered. The few data available do not present a clear picture regarding the radiogenicity of CLL, so it probably should not be ruled out. However we are concerned by the following issue: if the Japanese data include little information on the ERR of a cancer (because of small background rates) but the cancer is included, the upper confidence interval of the ERR in an analysis of that site alone (which could be large) fails to put into proper perspective what we know about that specific cancer and what we think is true about most tumors (that they are radiogenic to some degree, but not absolutely).

Reviewing the summary of risk estimates presented in table X of Thompson et al. (1994), we note that for a wide range of solid tumors there appears to be general homogeneity in dose-response relationships with a few obvious exceptions—only for digestive cancers (including stomach cancer) and cancers of the uterus (for which the risk estimate is negative) does the 95% confidence interval for the individual site fail to overlap the estimate of ERR (0.63/Sv) for all solid tumors. To formalize the impression of overall homogeneity in ERR, we conducted our own elementary meta-analysis of the data in table X of that paper, using methods described in DerSimonian and Laird (1986). Assuming that the 95% confidence intervals presented in table X have a length of roughly 4 standard errors (which is true asymptotically), we estimated the

standard errors of the risk for the various sites. Removing some obvious overlap in table X (between stomach cancer, colon cancer, and digestive cancers as a whole), we arrived at the ERR estimates and standard errors in table 1, appendix C.

A formal test for homogeneity of the relative-risk estimates in table 1 using the methods described in DerSimonian and Laird (1986) strongly rejects the hypothesis of homogeneity (chi-square = 78, 18 df, $p<0.0001$), but that is due principally to two cancer sites (cancers of the breast and of the uterus). Removing those and two other sites known to be strongly hormone-related (thyroid and ovary) reduces the evidence for nonhomogeneity of the ERR estimates in table 1 to marginal significance (chi-square = 22.6, 14 df, $p = 0.067$). The fact that there is relatively little evidence of heterogeneity for the remaining cancers suggests that information about them may indeed be pooled to describe the uncertainty in our estimate of ERR for any individual site. A formal way of doing this is also described in DerSimonian and Laird: the fitting of a random-effects model (a type of hierarchic analysis) and the calculation of posterior estimates of each site's ERR and confidence intervals. That is done in table 2, appendix C for the 15 non-hormone-related cancers.

Columns 2-4 reproduce the ERR estimates and lower and upper confidence intervals from table X of Thompson et al. (1994). Columns 5-7 give the predictions and 95% confidence intervals from the random-effects analysis; these were obtained with the hierarchic modeling program, MLn (appendix C gives the MLn program log). Note that the estimates from the random-effects analysis are all pulled toward a weighted average of the ERR estimates for the 15 sites (the weighted average was 0.44/Sv). And note especially the results for rare sites, such as kidney. The upper confidence interval of the ERR for this site was 2.2 ERR/Sv in Thompson's analysis, but the lower confidence interval was less than zero. In the random-effects analysis the breadth of the confidence interval is reduced by a factor of 3.6, with the upper limit now equal to 0.82 ERR/Sv. Such an uncertainty estimate appears to the members of the subcommittee to be in

line with the reason why kidney cancer should be considered for compensation at all: although the data on kidney cancer are somewhat equivocal and provide no significant evidence of a dose-response relationship, there is no evidence that it differs broadly in radiogenicity from other solid tumors. Placing it on the list of allowed tumors is not based purely on the data on this one site, but rather is informed by our general perceptions concerning solid tumors as a whole. Correspondingly, the upper confidence interval should not be based purely on the data for this one site, but should also reflect the same general findings.

We recognize that the above analysis is grossly simplified, since effects of age at exposure and time since exposure clearly will complicate a complete hierarchic analysis. Nevertheless, we feel that it is important in the case of rare tumors for the data on specific sites to be supplemented by what is known about other sites, and we believe that a random-effects analysis provides a reasonable, albeit largely pragmatic general framework. Accordingly, we suggest that the Working Group consider a hybrid analysis conducted as follows: a single summary ERR risk estimate for each of the nonradiogenic-cancer sites should be prepared as in table X of Thompson et al. (1994). A random-effects analysis of the summaries could be conducted (by the methods of DerSimonian and Laird) to combine broadly homogeneous sites (such as all non-hormone-related solid tumors). For a given site, the ratio, r, of the breadth of the confidence interval from the random-effects analysis compared to that from the analysis conducted separately for the site would be calculated (for kidney cancer, $r = 0.28$). This factor, r, then should be used as a deflation factor to reduce the range of confidence intervals derived for age-specific estimates of ERR by using the data on that tumor alone.

The subcommittee believes that the hybrid analysis is a useful strategy and has a wide application. Although there may be other approaches as well, the important thing is to find a way to deal with the anomalies that the exceedingly broad confidence intervals present.

The subcommittee believes that some allowance for uncertainty is appropriate once a population association is established, particularly if an agency has a stated policy to give claimants the benefit of doubt. However, even under a policy that aims at equity in that there should be a reasonable balance between "false-positive" and "false-negative" decisions, we believe that uncertainty needs to be considered by using the full probability distribution produced by uncertainty-propagation methods like that used in IREP. For example, one might consider a scheme that pays in proportion to the posterior probability that PC is greater than 50% or in proportion to the expected value of PC. Such schemes tend to be more equitable than simple all-or-nothing decisions based on the point estimate of PC or some upper confidence limit.

11. CONCLUSIONS AND RECOMMENDATIONS

Utility of Data Sources

Conclusion

- The working group has consistently used the best sources available on the magnitude of radiation effects, modifiers of radiation risk, baseline rates of disease, and other factors. When sources were unavailable or inadequate, it has made reasonable judgments in modeling parameters and their uncertainties. Risks of lung cancer posed by radon could not be assessed from the atomic-bomb survivor cohort, but a well-established risk model based on many cohorts of underground miners is available (NRC, 1999).

Recommendations

- Sources of data for modeling uncertainty in the RBE for neutrons and modeling the systematic biases in the gamma and neutron dose estimates need to be explained and discussed.

- A module for computing ASs for lung cancer in radon-exposed people would be a valuable addition, as opposed to waiting for the next update.

- The basis of the uncertainty distributions for the DDREF should be described and justified.

Assumptions Concerning Radiologic Effects

Conclusion

- The working group has used assumptions concerning radiologic effects that reflect the judgment of authoritative groups on radiation risk assessment. The subcommittee supports its approach and choices.

Recommendations

- The dose-response coefficients and their confidence limits for each tumor type are key elements of the AS assessment. The working group's report should include a table to provide this information.

- The subcommittee recommends that the working group's report include a summary table of each radiologic assumption, including a brief, nontechnical description, central estimates of the factors, and uncertainty parameters.

- It is recommended that a summary table be developed to compare the 1985 and 2000 AS results for a number of scenarios and tumor types. It should be accompanied by text that explains the main sources of differences between the two sets of results.

- In many compensation settings (such as worker exposures), it might not be clear for a given measured exposure whether the acute- or protracted- (chronic) exposure option should be used (or whether it should be a mixture of the two). The working group needs to provide more information on the use of the chosen option and might want to consider providing an option to model a mixture of acute and chronic exposures for a given measurement.

- It is suggested that the working group reevaluate its decision to use time-since-exposure as a modifier of AS only when there is a linear temporal slope. Several tumor types show nonlinear temporal trends that might need to be considered.

- The working group should consider how to transport PC calculations to minority populations in the United States when minority group's baseline rates differ appreciably from the average US rates. In principle, this is similar to the problem of transporting risk estimates from the Japanese to the US population. The subcommittee recognizes that the transport of PC calculations is compromised by the difficulty of obtaining reliable estimates of causality in subpopulations on which the data are inadequate.

Epidemiologic and Biostatistical Models

Conclusions

- In general, the biostatistical methods used to analyze the epidemiologic data from the atomic-bomb survivors are appropriate.

- The working group's treatment of the large number of tumor sites for which no significant dose-response pattern has been found in the Japanese data is of concern. These are described in the working group's report as constituting almost half the tumor sites considered. The inclusion of such tumors in the current report is a major departure from the 1985 report, in which only sites with statistically significant dose-response relations were considered. The subcommittee supports the view that these tumors ought to be included in some way, but we think that using separate analyses for each of the tumors has unfortunate practical side effects, particularly with regard to how the VA has tended to use upper confidence limits as criteria for compensation. Moreover, the use of methods for deriving an AS in this setting can lead to the false impression that such calculations have the same scientific rigor as those associated with tumors that have been shown to be radiogenic. This would have important

policy implications which should be considered by the appropriate agencies that would use these tables.

- The subcommittee notes that the AS calculation can be a biased estimate of personal PC when there is heterogeneity in baseline rates of cancer. We do not, however, adopt the position that one can expect extreme heterogeneity in baseline rates a priori. Analysis of monozygotic (MZ) and dizygotic (DZ) twins' data, for example, tends to show important, but far less than complete, dependence of risk of cancer on either genes or shared environment. Simulation studies indicate that even large variations in baseline rates lead to a high correlation between AS and personal PCs.

Recommendations

- The subcommittee suggests that tumors without demonstrated radiogenicity be analyzed in three ways and that the results of the three analyses be pooled to assign an ERR estimate for each diagnosis: as a single combined group with a single dose-response relation fitted to the occurrence of all such tumor; as a part of the group of all solid tumor; and combined with anatomically similar cancer sites. Uncertainty analysis should reflect the uncertainty in assigning ERR estimates so obtained to specific diagnoses. More generally, we suggest future consideration of hierarchical methods for estimating dose-response relations.

- The subcommittee recommends that AS calculations be performed for nonmelanoma skin cancers; information regarding the baseline rates in the United States is needed to use the transportation algorithm described in the working group's report. These skin cancers are not reportable in the United States, so routine SEER data are unavailable; but various surveys provide sufficient information for transportation (perhaps incorporating uncertainty into the baseline US rates) to be attempted.

- Further work on modeling the likely bias in AS due to genetic or environmental differences in an individual's cancer susceptibility (on the basis of whatever data exist on familial aggregation of cancer diagnoses, for example) might ultimately serve as a useful adjunct to the working group's report. However, we do not recommend that corrections for such biases be included in its current report, given the difficulties in assessing the variability of individual baseline rates.

Handling of Uncertainty

Conclusions

- The working group propagated the uncertainty of the estimate of ERR and associated AS by applying Monte Carlo methods to the estimated distribution of each of the parameters rather than combining lognormal distributions around point estimates for those parameters, as was done in the 1985 radioepidemiological tables. That has the advantage of allowing more flexibility in describing the uncertainty distribution around each parameter and in combining uncertainty distributions, although the assumptions on which it is based differ from those of the previous method. The subcommittee supports this approach but notes that the assumptions and methods of the approach must be stated clearly.

- The subcommittee was uncomfortable with the formulation of the residual "scale factor". Although we recognize the intention of capturing unspecified sources of bias and uncertainty about which we have no useful information, we believe that it is inappropriate to specify a distribution for unspecified factors. We do see the utility of including an option for users to specify an additional uncertainty factor if an appropriate justification is provided.

- The working group chose to evaluate AS for several anatomic sites for which there is no statistically significant dose-response pattern, in contrast with the approach used for the 1985 report. The subcommittee supports this in concept but is concerned about its

implementation. The analyses for some of those sites were based on relatively few events. Therefore, even if point estimates were large enough to suggest an important effect, the confidence intervals were so broad because of sample size that the effect was not significant. A result that is not statistically significant can be interpreted inappropriately as evidence of no effect.

- The subcommittee observed some processing problems when the "uncertainty setup" window was accessed and options changed. It is important for the user to be able to choose alternative options in this window and have the program still perform the appropriate calculations. It is also important that the random seed used for the simulation program change with each run unless a user specifies that it be constant for a series of runs. Currently, the values in this table are not recalculated unless a user changes the inputs. Clicking the button after closing the window has the effect only of reopening the window. The same is true of the "preceding results" button that shows the inputs and the ERR. To recalculate, users have to change the inputs. That means that someone who runs a case will always get the same answer until another case is run; returning to the first case will now yield identical answers. It also seems; however, that the seed is reset whenever ANALYTICA starts, so by running the same sequence of cases one would generate consistent answers.

Recommendations

- The assumptions and methods implicit in the use of Monte Carlo simulation methods (such as the independence of each of the parameters) and their implications relative to the 1985 methods should be stated clearly.

- To elucidate the differences in the estimated AS values in the current working group's draft report from the 1985 report, the subcommittee recommends that a more extensive comparative analysis of the IREP program output be conducted than has been done for the current draft report. It could be implemented as a factorial evaluation over a reasonable sample of values for each of the parameters, and the resulting AS values could be presented

in parallel with estimates from comparable scenarios based on the 1985 tables. The analysis should be included in tabular form in the final report.

- The subcommittee recommends changing the name of the residual "scale factor" to "additional uncertainty factor" and setting its default value to 1.0 so that it will not affect the calculations unless a user alters it. If a user wishes to include an additional uncertainty factor, the program should force the user to name the factor to make clear what variation it represents and then to specify its GSD. It is to be hoped that the user would justify the inclusion of the factor and the magnitude of the GSD, so that the factor is not used capriciously.

- The working group should make sure that when, in the "uncertainty setup" window, a user changes the number of iterations in the simulation, the sampling method, the randomization method, or the random seed, the program performs the appropriate simulation when any of the "Calc" buttons are selected. As it is, when these values are changed, none of the "Calc" buttons functions properly.

- It is important that the random seed used in the simulations change with each successive run of the program unless a user specifies that it remain constant. The program should set as a default that this value change and should create an option to freeze the value of the random seed.

- In the selection of sample size in a simulation, the default is set to 1,000. That does not yield particularly stable predictions of the 99th percentile AS value for at least some cancer sites. We recommend that either it be set higher or, because size is a user option, users be strongly encouraged to do so in dealing with rare cancers.

Suggestions

- To evaluate the importance of cancer sites for which the number of events is relatively rare, the subcommittee suggested above that future evaluations use either hierarchic random-effects models or Bayes model averaging to capture the possible dose-related effect at each

site better. In the interim, to increase the sample size, the working group could consider grouping all these sites for a single analysis or combining each of the sites with its larger organ system. The subcommittee notes that this suggestion also has relevance to the issue of uncertainty in the estimates of PC (or AS).

- To make it easier to calculate AS for a set of subjects or exposure scenarios, the subcommittee suggests that IREP be modified to allow batch processing. If that suggestion is implemented, a user could create a file in which each record reflects the characteristics of a single subject and his or her exposure history. The program would use this file as input, would process all records in the file, and would create a tabular output file reporting selected percentiles of AS, components of AS, and components of the adjusted ERR per sievert.

Making the Radioepidemiological Tables Available to the Public

Conclusions

- The revised tables have the potential to be more useful and accessible to a broader audience than the existing tables. Nonetheless, it would be unfortunate if the working group sacrificed any of the benefits of the current tables.

- The IREP program is an important first step in making the information in the revised tables more broadly and effectively available and useful.

- A purely technical presentation of the revised tables will be inadequate to meet the needs of all potential users. In its current state, the program cannot be effectively used by persons who lack familiarity with computers or with the calculation of AS. A novice in either case would have difficulty navigating the program.

- Distribution of software, whether on the Web or by other means, imposes specific additional requirements for effective dissemination. In particular, the software must explicitly address the issues of availability, transparency, flexibility, and suitability for its likely audiences.

- The statistical assumptions (and underlying policy decisions) embodied in the tables might not be clear to new (or even existing) users.

Recommendations

- The revised tables should be made available in a variety of forms and distributed through a variety of mechanisms, including a printed version of the tables analogous to the 1985 document for audiences that would prefer this to computerized delivery.

- A public summary should be developed and made available broadly. It should include a glossary of terms and concepts for nontechnical audiences, should clearly describe and give the reasons for the changes from the 1985 tables that are embodied in the revised tables, should include an explicit table comparing the results of the 1985 and 2000 procedures for comparable cases, and should describe the process for future revisions plainly.

- The revised tables, in all forms, should include a clear presentation of the statistical assumptions that are made and the policy implications of the assumptions. The presentation should be in language and use examples that will be understandable by a lay audience. An important part of the presentation is to distinguish between PC (AS) and risk. And it must state clearly that the revised tables cannot be used to estimate risk or to predict the development of any cancer.

- There should be an intelligible but simple presentation of the details of implementation (what are the levers that drive the actual results?). The current draft report, although adequate for a technical audience, will need modification for other constituencies.

Suggestions

- The IREP software needs additional development if it is to be useful to broader audiences. If broad availability is pursued, the working group should give further consideration to how the software will be made accessible to the public, including not only mechanisms of

distribution, but also user-friendliness. Planning for this dissemination of the program and the revised tables should include adequate representation of lay stakeholders; making the program's operation more transparent to the user (the documentation described in the preceding recommendation can serve as the basis for this); and ensuring flexibility of the program to accommodate user input for variables and procedures not fixed by law, policy, or scientific consensus and identifying the ones that are so fixed.

- The use of the Web to disseminate and support the revised tables needs to be carefully considered. If the working group elects to pursue this option, guides should be constructed for audiences that do not regularly access the Web, a non-Web means of notifying potential audiences about the Web site and alternative access mechanisms should be developed, an adequate plan and budget for technical support of the Web site and other mechanisms must be developed if Web distribution is to succeed, and great care will be needed to address the privacy concerns of users if the program is implemented as an interactive Web application.

- The computer software ought to inform the user that his or her cancer could be one of the cases that make up the large natural incidence of cancer in the United States, one of the cases of that cancer due to other causes, induced by medical radiation, or induced by natural background radiation.

12. SUGGESTIONS FOR FUTURE COMPENSATION POLICY

Current compensation policy is based on the tort-law principle of preponderance of evidence, which has been widely interpreted, as requiring that a claimant's estimated probability of causation be at least 50%. The subcommittee has some misgivings about this approach to settling claims. It makes no explicit provision, for example, in the uncertainty inherent in the PC estimate itself. However, a reasoned approach to compensation for cancers possibly caused by prior exposure to ionizing radiation should follow the rules for rational decision-making under uncertainty. Those rules demand that uncertainties of possible outcomes be specified and that the various consequences of actions be described in terms of utilities (Lindley, 1985). Such an approach to compensation is missing and needs to be developed. The subcommittee notes, too, that

- The all-or-none threshold can lead to substantial differences in the treatment of individuals with minimal differences in their true PCs. Here the subcommittee is not suggesting the 50% probability as a "bright line" cutoff, but rather the award of compensation on a sliding scale depending on the posterior probability that the PC exceeds 50%, on the bases of its uncertainty distribution.

- Theoretical arguments have demonstrated that unobservable heterogeneity between individuals can lead to a downward bias in the epidemiologically derived AS as an estimator of the average of individuals' PCs and that the magnitude of this bias will vary across individuals in a way that depends on such factors as age, dose, and unobservable baseline risk.

- PCs cannot be estimated with certainty, but the distribution of their possible values can be derived on the basis of reasonable assumptions about the remaining components of uncertainty, such as those implemented in the current IREP program, and such uncertainty needs to be taken into account in resolving claims.

- The PC-based approach to compensation takes no account of the loss of life expectancy experienced by claimants at the stage of deciding whether to make an award, but only perhaps at the stage of choosing the magnitude of the award once such a decision has been reached.

Several alternatives have been suggested, including the following:

- The use of payment schemes on a sliding scale, such as the one that has been used by British Nuclear Fuels Ltd for over a decade.
- Compensation schemes based on the estimated loss of life expectancy attributable to exposure.
- Consideration of the distribution of uncertainty in reaching decisions.

The subcommittee suggests that such alternatives be considered by the appropriate agencies. In other words, the subcommittee does not advocate a specific compensation system, but suggests that agencies involved in compensation claims review the systems that they use to avoid inequities in their procedures.

APPENDIX A

Specific Comments on the Working Group's Draft Report

p. 13, line 2: Clarify whether the excess risk, excess relative risk, or some other measure was assumed to be lognormally distributed over time since exposure.

p. 13, section 5, line 5: The reference to section II.C.1 appears to be incorrect.

p. 14, line 3: Why would risk 5-14 years after exposure have been overestimated?

p. 16, section B, last sentence: Is there any reason to be concerned about possible differential ascertainment by calendar time or dose?

p. 20, section 2 ff: Although the discussion of whether radiation accelerates the appearance of cancer or increases the risk is relevant to some of the points made by Robins and Greenland, a more fundamental issue is the bias in AS as an estimator of the mean of individual PCs produced by heterogeneity in *baseline* rates. This point is discussed elsewhere in the National Research Council Oversight Committee's report, but merits some discussion in the working group's report.

p. 29, lines 2-3 after the formula: The g following β should be omitted because it is not the parameter, but the observed covariate value (sex).

p. 32: In analyzing the Japanese atomic-bomb survivor data, very little uncertainty in neutron RBE is allowed. That seems incongruous with the current debate over neutron RBEs in

that study and with the wide range of findings in the experimental literature regarding neutron RBEs.

pp. 32-33: No indication is given of what the "systematic biases" in the atomic-bomb dose-estimation procedure consist of.

p. 34: No justification is given as to why 5 hours is the critical value to distinguish acute from fractionated exposures in the assigned-shares model.

p. 37: Figure IV.F.3 might be easier to interpret if presented in terms of the dose-response curves themselves, that is, $1 + \beta D \times DDREF_{acute}(D)$.

p. 37 and elsewhere: The mode of presentation (especially graphic) of the DDREF is counterintuitive and might confuse many people who are not conversant with the lingo of radiobiology. One normally thinks of a "factor" as multiplicative or additive, but in the case of DDREF it is a division factor. It would be better to plot 1/DDREF (to show that a higher DDREF yields *less* effect, not *more*, as the graph seems to imply). Text should be added on p. 33 to clearly indicate that, for example, a DDREF of 2 implies half as large a slope.

p. 41: Arguably, one should attach some uncertainty to the low-LET doses, because gamma exposures are believed to have a slightly lower RBE than 250-kVp x rays, and low-energy x rays are thought to have a higher RBE than 250-kVp x rays.

p. 46, section 2: Did Land and others [1994] restrict their analyses to age at first full-term pregnancy, or were the other standard breast-cancer risk factors also examined? How

was this variable coded for nulliparous women? Even though these authors adopted the parameterization given here, elsewhere in this report $\theta = 1$ corresponds to the multiplicative model and $\theta = 0$ to the additive model. Perhaps internal consistency would be less confusing.

p. 47, last paragraph: The three references to tables IV.G should be to tables IV.I. Some discussion of the literature on alternative forms of mixture models (such as, multiplicative, Guerro-Johnson, and Box-Cox models) might be worth while.

p. 49, section J: The possibility of an interaction of the ATM gene with ionizing radiation should be mentioned here. Although experts differ about the ATM-radiation interaction, it would be right to raise the concerns that there is some controversy about it (Wong et al, 1997; Nichols et al, 1999; Shafman et al, 2000).

p. 49: It is doubtful that xeroderma pigmentosa patients have increased susceptibility to carcinogenesis induced by ionizing radiation, even though they are exquisitely sensitive to ultraviolet radiation. Did the authors instead mean nevoid basal-cell carcinoma syndrome patients who have a well-documented radiosensitivity?

p. 51, section 2: Why were these two situations excluded?

p. 53, section 5b: It seems inconsistent with the treatment of other uncertainties to fix the coefficient of D^2 at 1.0 as though it is known with certainty.

p. 54, section 7: The reference to section IV.G appears incorrect; was IV.D intended?

p. 70-76: It would be useful if these tables gave the 99th percentile estimate from the 1985 calculations for comparison with the new calculations.

APPENDIX B

Specific Comments on the Interactive Radio-Epidemiological Program

Most of the following comments deal with the potential for making improvements in the impressive start made by the design team. Sponsors will need to consider not only the policy, but also the budgetary, implications of these suggestions.

Some of the concerns of the subcommittee set forth here might reflect the design team's decision to implement the model in the proprietary modeling-spreadsheet program ANALYTICA, rather than coding it directly. We recognize that there are savings in development expense if one uses this type of environment. However, the savings often mean that the model developer has less flexibility in preparing the user interface. Accordingly, some of our suggestions, particularly regarding system appearance and convenience, could be too difficult or too expensive to implement. Ultimately, their value depends on the size and nature of the user base. As stated above, the information supplied by the developers indicates that the primary target audience is small and familiar with the underlying logic of the system. However, careful consideration needs to be given to other potential audiences, particularly those for whom the process is not well understood but who have a substantial stake in the outcome. The developers clearly were aware of this design consideration, but the design as implemented is only partially successful in addressing the broader stakeholder community. In particular, key features of a system to meet stakeholder needs might be difficult to implement if only the "browser" version of ANALYTICA is available to users.

Some of the ensuing comments reflect the interim nature of the development system and will not necessarily apply to a final implementation.

Installation

Given that the installation appears to use Install Shield, it should be possible to install the IREP files and the ANALYTICA browser module in a single operation. That would make the system a little easier for computer novices.

The version of ANALYTICA that is used is a trial version. Is there a simple browser version that can be installed without requiring the user to face the registration screen?

The setup program runs fine off the CD. Why is the user instructed to copy it to the hard drive?

ANALYTICA Constraints

It is mildly annoying that ANALYTICA does not appear to support the wheel mouse.

Some buttons appear to work on a single click; others require a double click. It is not intuitive in advance which are which. Double-clicking on a single-click button drops the user into an empty (blank) window.

The redrawing of windows has some problems. In addition, ANALYTICA sometimes opens windows in odd locations; some have to be dragged back to the screen center for closing.

The display of scroll bars is somewhat insensitive to completeness of display: they imply that a window contains more than is shown, whereas all window content is visible.

Many more objects are selectable than is desirable in a system that will support inexperienced users. For example, clicking practically anywhere in the screen calls up a definition. Ideally, one wants to control all the selections that a user can make. Similarly, many of the menu-bar and tool-bar choices are of little interest to the user, as opposed to the system designer. Can they be suppressed or activated selectively?

The cursor is uninformative about what one can and cannot operate: some things look like jumps but do not go anywhere.

IREP Choices in Implementation

The use of an edit table for names and reference number is not particularly intuitive. Also, the system is not apparently creating any kind of index of multiple runs with these data. If these were only labels, an editable text box would give the user an easier job, more flexibility, and less concern.

Year edits are inconvenient and counterintuitive. A count-up and count-down boxes would make the user's life easier. Hitting <Enter> (the most intuitive keystroke after typing a value), rather than registering the user's choice instead adds a blank line to what should be a one-line field.

Edit tables carry information from the previous case instead of zeroing out when starting a new case. By entering a male who was born in 1952 with diagnosis in 2000 and indicating five exposures, the system preselected 1955 as the first exposure. Also, edit tables are not closed by the clicking of the green check (an expected outcome for users of this icon). Again, the transposition options on edit tables are of uncertain value; they seem to add considerable visual complexity without addressing a user need.

Input Data

Note the discussion of date issues under "Accessibility". Working on age rather than year would eliminate a user entry.

Dose-input information might be the least user-friendly aspect of the system, particularly if distributional data are expected to be the norm. The user should not be asked to type in a distribution name and parameters, but rather at a minimum should be offered a drop list and count-up and count-down boxes for parameters. Also, it seems awkward to have to provide the

doses and dates on separate tables, inasmuch as when the two would naturally be lined up together in a single table.

Serious consideration needs to be given to both the numerical and physical forms of the data received by expected users. Will the people responsible for adjudicating compensation claims for radiation-related cancer have dose information that describes a particular distribution, or are they expected to infer one? Do the data come in on paper or electronically? Related to this problem is the absence of error checking on data entry. The user gets well into the analysis before the system crashes with bad data.

APPENDIX C

Supplement to Text

The following two tables and the software supplement the text in chapter 10 "Future Revisions and Broader Issues", section "Role of Uncertainty in Compensation".

Table 1. Summary of Table X (from Thompson et al., 1994)

Site	ERR/Sv	Std Err
Oral	0.29	0.255
Esophagus	0.28	0.3025
Stomach	0.32	0.085
Colon	0.72	0.2525
Rectum	0.21	0.23
Liver	0.49	0.19
Gallbladder	0.12	0.2475
Pancreas	0.18	0.2675
Respiratory	0.8	0.175
Trachea	0.95	0.2
Skin	1	0.3725
Breast	1.6	0.275
Uterus	-0.15	0.0975
Ovary	0.99	0.545
Prostate	0.29	0.3525
Bladder	1	0.4575
Kidney	0.71	0.5775
Nervous system	0.26	0.3825
Thyroid	1.2	0.405

Table 2. Random-Effects Analysis of Sites in Thompson et al. (1994) Table X

	Thompson et al. Analysis			Random-Effects Analysis Posterior estimates		
Site	ERR/Sv	Lci	Uci	ERR/Sv	Lci	Uci
Oral	0.29	-0.09	0.93	0.42	0.14	0.70
Esophagus	0.28	-0.21	1	0.43	0.13	0.73
Stomach	0.32	0.16	0.5	0.35	0.19	0.51
Colon	0.72	0.29	1.3	0.55	0.27	0.84
Rectum	0.21	-0.17	0.75	0.38	0.11	0.66
Liver	0.49	0.16	0.92	0.48	0.23	0.74
Gallbladder	0.12	-0.27	0.72	0.36	0.08	0.64
Pancreas	0.18	-0.25	0.82	0.39	0.10	0.68
Respiratory	0.8	0.5	1.2	0.64	0.39	0.88
Trachea	0.95	0.6	1.4	0.68	0.42	0.94
Skin	1	0.41	1.9	0.57	0.26	0.88
Prostate	0.29	-0.21	1.2	0.44	0.14	0.75
Bladder	1	0.27	2.1	0.54	0.23	0.86
Kidney	0.71	-0.11	2.2	0.50	0.17	0.82
Nervous system	0.26	-0.23	1.3	0.44	0.13	0.75

MLN - Software for N-level analysis.

```
Note --- read in data
dinp to c1-c4
250000 spaces left on worksheet

Type file name
->
solid.dat
1 2 0.29 0.255
1 4 0.28 0.3025
1 5 0.32 0.085
1 6 0.72 0.2525
1 7 0.21 0.23
1 8 0.49 0.19
1 9 0.12 0.2475
1 10 0.18 0.2675
1 11 0.8 0.175
1 12 0.95 0.2
1 13 1 0.3725
1 17 0.29 0.3525
1 19 1 0.4575
1 20 0.71 0.5775
1 21 0.26 0.3825
name c1 'cons' c2 'lineno' c3 'rr' c4 'stderr'
iden 1 'lineno'
iden 2 'cons'
expl 'cons'
resp 'rr'
setv 1 'cons'
note --- set variance offset (var of estimate of err
offset 1 from c4
note setv 2 'cons'
batch 1

Batch mode is ON
tole 3
maxit 20
note -- fit model
start

Convergence achieved
note -- display model results
rand
```

```
LEV. PARAMETER    (NCONV)  ESTIMATE  S. ERROR(U)  PREV. ESTIM   CORR.
-------------------------------------------------------------------------
 1  CONS    /CONS    ( 1)   0.02878     0.02942      0.0288
fixed

PARAMETER     ESTIMATE   S. ERROR(U)  PREV. ESTIMATE
CONS            0.4798      0.07837         0.4798
note -- use model results to form reliability coefficient rho
calc c41=0.02978+c4*c4
calc c41=0.02978/c41
names c41 'rho' c11 'predict'
note -- form predictions based on estimated err, and rho
calc c11='rho'*'rr'+(1-'rho')*0.4798
note -- form variance of model predictions
note -- as var(rand_eff)*(1-rho)+var(fixed effect)
calc c21=0.0279*(1-'rho')+0.02942*0.02942
calc c21=sqrt(c21)
names c10 'RandEff' c11 'Predict' c20 'VarRE'
names c21 'stdev_p'
print 'lineno' 'Predict' 'stdev_p' 'rr' 'stderr'

     LINENO      PREDICT     STDEV_P      RR        STDERR
N =    15           15          15         15          15
   1  2.0000     0.42018     0.14143    0.29000     0.25500
   2  4.0000     0.43074     0.14804    0.28000     0.30250
   3  5.0000     0.35120     0.079453   0.32000     0.085000
   4  6.0000     0.55627     0.14101    0.72000     0.25250
   5  7.0000     0.38262     0.13681    0.21000     0.23000
   6  8.0000     0.48441     0.12710    0.49000     0.19000
   7  9.0000     0.36210     0.14014    0.12000     0.24750
   8  10.000     0.39170     0.14341    0.18000     0.26750
   9  11.000     0.63766     0.12252    0.80000     0.17500
  10  12.000     0.68047     0.12984    0.95000     0.20000
  11  13.000     0.57172     0.15439    1.0000      0.37250
  12  17.000     0.44311     0.15288    0.29000     0.35250
  13  19.000     0.54459     0.15903    1.0000      0.45750
  14  20.000     0.49867     0.16272    0.71000     0.57750
  15  21.000     0.44263     0.15507    0.26000     0.38250

note now do likelihood ratio test for nonzero variance
like 249891 spaces left on worksheet

-2*log(lh) is     7.70057
dinput to c41
```

```
249891 spaces left on worksheet

Type file name
->
small.txt
1 .001
rcon c41
maxit 100
next

Convergence achieved
like
249904 spaces left on worksheet

-2*log(lh) is      10.0264

stop
```

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WILLIAM J. SCHULL, Ph.D., (Chair), is Ashbel Smith Professor Emeritus. His specialty is human genetics and his primary research interest is radiation biology. In addition to a distinguished academic career, Dr. Schull previously served as the Head of the Department of Genetics with the Atomic Bomb Casualty Commission (ABCC) in Japan and later went on to become one of the Directors of the ABCC's successor organization, the Radiation Effects Research Foundation. Dr. Schull is the recipient of numerous awards, including Japan's Order of the Sacred Treasure, Third Class. Dr. Schull is a member of several professional societies including the American Epidemiological Society, the American Society of Human Genetics, the Radiation Research Society, and the Society for the Study of Human Biology.

SHARON M. FRIEDMAN, MA, is the Iacocca Professor and Director of the Science and Environmental Writing Program, at Lehigh University. She served as Chairperson of the Department of Journalism and Communication at Lehigh from 1986-1995. Her research focuses on how scientific, environmental, technological, and risk issues are communicated to the public. She served as a consultant to the President's Commission on the Accident at Three Mile Island and the United Nations Economic and Social Commission for Asia and the Pacific (ESCAP). She co-authored the book *Reporting on the Environment: A Handbook for Journalists*, which has been translated into 11 languages and widely distributed. She has lectured in many Asian countries sponsored by ESCAP and other organizations about risk communication and environmental journalism and served as a Fulbright Distinguished Lecturer in Brazil. Professor Friedman is the co-editor of *Communicating Uncertainty: Media Coverage of New and Controversial Science and of Scientists and Journalists: Reporting Science as News*. She is an Associate Editor of the journal *Risk: Health, Safety & Environment*, and a member of the Editorial Advisory Board of the journal *Science Communication*. She is a Fellow of the American Association for the Advancement of Science (AAAS) and a member of the Committee on Council Affairs and the Council of the AAAS.

PETER G. GROER, Ph.D., is Associate Professor in the Department of Nuclear Engineering at The University of Tennessee-Knoxville. Dr. Groer earned his Ph.D. in Theoretical Physics from the University of Vienna, Austria. He teaches undergraduate and graduate courses in Radiation Protection, Radiation Risk and Reliability Analysis. His research interests include Bayesian methods for radiation detection, dosimetry, and risk and reliability analysis. He has served on the editorial board of Risk Analysis. He was a member of the National Research Council's (NRC) Committee on the Health Effects of Radon and Other Internally Deposited Alpha Emitters (BEIR IV) and served on several scientific committees of the National Council on Radiation Protection and Measurements. He was also a member of the EPA Science Advisory Board's Uncertainty in Radiogenic Risks Subcommittee and of the NRC Committee on the Exposure of the American People to I-131 from Nevada Nuclear-Bomb Tests.

SUSAN E. LEDERER, Ph.D., teaches in the Section of the History of Medicine at the Yale University School of Medicine and in the Department of History at Yale University. She received her doctorate in the history of science from the University of Wisconsin, Madison. Before going to Yale, she taught for a number of years in the Department of Humanities at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. A historian of American medicine, she served as a member of the President's Advisory Committee on Human Radiation Experiments in 1994-1995. The author of *Subjected to Science: Human Experimentation In America before the Second World War*, she has written extensively on issues related to human and animal experimentation. She is currently writing a social and cultural history of blood transfusion and organ transplantation in twentieth-century America.

ROY E. SHORE, Ph.D., Dr.P.H., is a Professor of Environmental Medicine and Director of the Epidemiology Program at New York University Medical School. Dr. Shore received his Ph.D. degree from Syracuse University in 1967 and his Doctorate in Public Health from Columbia University in 1982. His research interests include environmental and occupational epidemiology, radiation epidemiology, and epidemiologic methods. He is on the standing committees on radiation biology/risk assessment of both the International Commission on Radiological Protection and the National Council on Radiation Protection and Measurements. He has served on several scientific advisory groups for the National Cancer Institute, Department of Energy and the Environmental Protection Agency, and on editorial advisory boards of the *Journal of the National Cancer Institute*, and *Cancer Epidemiology, Biomarkers and Prevention.*

DANIEL O. STRAM, Ph.D., is an Associate Professor in the Department of Preventive Medicine at the University of Southern California. Dr. Stram earned his Ph.D. in Statistics from Temple University, and engaged in postdoctoral research in Biostatistics at the Harvard School of Public Health. From 1986-89 he was a member of the Statistics Department of the Radiation Effects Research Foundation in Japan. Since 1990, Dr. Stram's research interests have focused on clinical research and epidemiology in childhood and adult cancers at the University of Southern California and the Children's Cancer Group. His radiation-related work in Hiroshima and U.S.C. has concentrated on statistical aspects of dosimetry systems used for the A-bomb survivors and for the U.S. Uranium miner cohort study. Dr. Stram is a member of the Board on Radiation Effects Research (BRER) of the National Research Council.

DUNCAN C. THOMAS, Ph.D., is Professor of Preventive Medicine, Director of the Biostatistics Division, and Verna R. Richter Chair in Cancer Research at the University of Southern California School of Medicine. His primary research interest has been in the development of statistical methods for cancer epidemiology, but he also has wide ranging interests in both environmental and genetic epidemiology. On the environmental side, he has been particularly active in radiation carcinogenesis, having collaborated on studies of cancer in residents downwind of the Nevada Test Site, uranium miners, medical irradiation, and the atomic bomb survivors. He was a member of President Clinton's Advisory Committee on Human Radiation Experiments, as well as the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR V), and radiation advisory committees for numerous other

governmental agencies. Other environmental activities include studies of asbestos, malathion spraying in California, electromagnetic fields, and air pollution; he is Co-Director of the Southern California Environmental Research Center. On the genetic side, Dr. Thomas has numerous publications in the area of statistical genetics and is collaborating on family studies of breast, ovarian, colon, prostate and other cancers, insulin dependent diabetes, systemic lupus erethematosis, and other diseases. He chairs organizing committees for the Genetic Analysis Workshop and the Informatics Consortium for the NCI Cooperative Family Registries for Breast and Colorectal Cancer, and is currently President of the International Genetic Epidemiology Society. These three broad areas of interest make him uniquely qualified to address methodological challenges in studying gene-environment interactions.

DANIEL WARTENBERG, Ph.D., is a Professor in the Department of Environmental and Community Medicine at the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey. He is also the Chair of the Doctoral Program in the New Jersey Graduate Program of Public Health. Dr. Wartenberg's main research interest is the development and application of novel statistical approaches to the study of environmental risk, pollution, and public health, with particular emphasis on geographic variation and clustering. He has conducted research on health effects of incinerators, exposure to pesticides and toxic chemicals, risk assessment methodology, and currently is conducting a study characterizing populations living near high voltage electric transmission lines.

JOHN S. YOUNG, Ph.D., President of Hampshire Research, is a toxicologist and risk assessor with extensive experience in toxic chemical policy issues. He has served as the chief scientist for the research effort that designed the RISK*ASSISTANT software system, and is currently directing the LifeLine Project to develop software for aggregate and cumulative exposure and risk assessment. He directs the community technical assistance program, assisting lay audiences in the interpretation and use of scientific information. Dr. Young has also been the author of numerous studies for the U.S. EPA, other state and federal government agencies, the United Nations and other multilateral organizations. Prior to joining Hampshire, Dr. Young served on the faculty of the Department of Environmental Health Sciences at the Johns Hopkins School of Hygiene and Public Health.