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Science Panel Report No. 3 & 2

REVIEW OF THE REPORT OF THE NATIONAL INSTITUTES OF HEALTH AD HOC WORKING GROUP TO DEVELOP RADIOEPIDEMIOLOGICAL TABLES

January 1985

Committee on Interagency Radiation Research and Policy Coordination

Office of Science and Technology Policy
Executive Office of the President
Washington, D.C. 20506

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

NOTICES

This report was prepared under contract DE-AC05-760R00033 between the U.S. Department of Energy and Oak Ridge Associated Universities.

*Departments of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, Housing and Urban Development, Interior, Justice, Labor, State and Transportation; Environmental Protection Agency, Federal Emergency Management Agency, National Aeronautics and Space Administration, Nuclear Regulatory Commission, Office of Management and Budget, Veterans Administration and the National Security Council.

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COMMITTEE ON INTERAGENCY RADIATION RESEARCH
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JUN 01 1985

Alvin L. Young, Ph.D.
Senior Policy Analyst
For Life Sciences
Chairman, CIRRPC
Executive Office of the President
Office of Science & Technology Policy
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Dear Al:

Enclosed is the Science Panel Report on the January, 1985, "Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables." This Science Panel Report was approved by the Science Panel on June 1, 1985.

The report was prepared for the Science Panel by a subpanel whose membership is: J.W. Thiessen, Chairman; W.A. Mills; L.S. Myers; and B.W. Wachholz.

Sincerely,

Laurence B Hobar, M.D., Ph

for Randall S. Caswell, Ph.D.
Chairman, CIRRPC Science Panel

Enclosures

Preface

This report of the Science Panel supplements an earlier document (attached), which summarized the Panel's views on the September, 1984, draft Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables.

Before providing the additional comments concerning the final report of the Ad Hoc Working Group, dated January 4, 1985[1], the Science Panel wishes to emphasize two points.

First, although the Orphan Drug Act requires that tables be produced for a range of dose from one millirad to 1000 rad, the Working Group chose to make no estimates below one rad. The Science Panel is in agreement with this judgment because in the low-dose range there is little empirical evidence of a carcinogenic effect in humans.

Second, in order for the Tables to be applicable, a person must have both one of the cancers listed in the Tables and a previous exposure to ionizing radiation. Therefore, the Tables should not be applied to determine the likelihood that a person having received a specific radiation dose will have such a cancer.

The Panel's previous recommendations were primarily concerned with three issues:

- Use of Quality Factors,
- Use of tables for exposures from internally deposited radionuclides,
- Treatment of uncertainties.

In the final report, the Working Group has dispensed with the use of Quality Factors in treating the risks from internally deposited alpha emitters and has substantially expanded on its treatment of uncertainties. The Science Panel's comments on these changes and other aspects of the report follow:

I. Science Panel Report No. 3

A. Quality Factors

The Science Panel previously questioned the use of Quality Factors for expressing risks from high-LET radiation, such as neutron and alpha radiation. This problem is avoided in the final report by restricting Probability of Causation (PC) calculations for such radiations to two cases where epidemiological data exist, viz., for bone cancer induced by radium-224 and lung cancer induced by radon decay products. In the former case, the PC is given as a function of the absorbed dose; in the latter, it is a function of the Working Level Month (WLM) exposure, as suggested by the Science Panel. This restriction seems reasonable to us at this time in light of current efforts by a number of scientific and advisory bodies to evaluate the risks from neutrons and internal alpha emitters. In summary, we approve of the changes made and find the treatment of high-LET radiation in the final report to be responsive to our expressed concerns

B. Internally Deposited Radionuclides

Although an extensive database has been built up during the last few decades covering the effects of internal emitters in animals, the Working Group decided not to evaluate this source of information with respect to its applicability for the estimation of human risk. The Panel feels that this omission, though understandable in light of the heavy pressures of time exerted on the Working Group, should not be continued indefinitely, but that a beginning should be made in the short term with the examination and interpretation of this database (see recommendations below).

The Science Panel previously advised that the lung cancer risk associated with radon daughter inhalation be expressed directly in terms of WLM exposure rather than in terms of estimated dose. On the assumption of a multiplicative interaction between radiation dose from this source and smoking the Working Group has now adopted a relative risk coefficient of 1.2%/WLM. This is in contrast to the additive interaction with smoking postulated for low-LET radiation. In light of current data and analyses, this seems to be a reasonable way to treat the influence of smoking for these two very different kinds of exposures. The value of 1.2%/WLM also appears reasonable in light of current information.

In an earlier draft document, lung cancer risk estimates were drawn from those in BEIR III, which in turn were based on joint consideration of uranium miner and A-bomb survivor populations. In the final report, however, estimates for low-LET external radiation were made on the basis of the A-bomb survivor data alone, leading to substantially lower PC values for lung cancer. The Panel is in agreement with this change.

C. Treatment of Uncertainties

As suggested by the Science Panel, the treatment of uncertainty has been consolidated in Chapter VII. Also as suggested, more attention has been paid to quantifying the uncertainty. The early sections of the Chapter provide an excellent discussion of the various sources of uncertainty. Section O grapples with the difficult problem of combining the various sources to obtain an estimate of the overall uncertainty in the calculated PC value.

In Section O, each source of uncertainty is assumed to follow a log-normal distribution with a known variance and to affect relative risk multiplicatively. This approach breaks important new ground in the area of radiation risk assessment and provides a much needed perspective on the credibility of calculated PC values. Nevertheless, it should be recognized that not all sources of uncertainty are included in the computation, so uncertainties in the PC may be somewhat understated, particularly for certain cancers, as discussed below.

One omitted source of uncertainty is that associated with the sparseness in the data from which estimates of risk coefficients are derived. This statistical uncertainty is addressed in Table VII-3 on p. 106, which lists, for a number of sites of radiogenic cancer, 90% confidence limits on the absolute risk coefficient based on A-bomb survivor data. Where the database is relatively "good," the range of uncertainty is narrow: e.g., only +9% for leukemia However, where the observed excess is smaller relative to the expected cancer incidents, the uncertainty range may be much wider: e.g., for esophageal cancer, upper and lower bounds in the absolute risk coefficient differ by a factor of 15. Because this source of error was omitted from the Working Group's prescription for combining uncertainties (see pp. 96, 112-113), there

is an associated underestimation in the overall range of uncertainty for some cancers listed in the Tables. It should be noted, however, that for any cancer where the statistical uncertainty is large, the effect on upper and lower bounds of the PC will be asymmetric. In particular, although the lower bound may be decreased by a larger factor, inclusion of this source will generally increase the upper-bounds by less than a factor of two. For this reason, the Panel believes the omission is not very serious.

As stated previously, each source of uncertainty was assumed to be distributed lognormally. This may not be appropriate for some sources treated in Section O, e.g., that relating to the choice of a dose-response model. In as much as the handling of the diverse uncertainties is not straightforward, a complete analysis would appear to require some systematic way of incorporating subjective judgments as to the effect of alternative assumptions and parameter values

Finally, the discussion of "biassed uncertainties" on p. 95 might lead one to conclude that, as a consequence of projected changes in A-bomb dosimetry, the best estimate of risk for most cancers might be a factor of 1.62 times higher than that upon which the respective PC value in the Tables is based. This might cause some confusion as to what value should be assigned to the PC. The Science Panel would emphasize that the Tables, as constituted, reflect best estimates *based on current data*.

D. Recommendations for Future Revisions of the Table

In the next two or three years important new information is expected from the reassessment of A-bomb dosimetry, updating of the Life Span Survivor Study, the National Academy of Science's study of internally deposited alpha emitters and other related activities by various national and international scientific organizations (viz., the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements and the National Council on Radiation Protection and Measurements) The Panel believes that a revision of the Tables should begin when these results become available. The revision should include, in addition to a review of the new data, a reexamination of both the models used for estimating risk and the methods used for treating uncertainties.

The Science Panel recommends that, in the interim, a committee be assembled to specifically address the applicability of the existing animal database on the exposure and effects from high- and low-LET radiation emitting radionuclides for the estimation of human risks from internal emitters. If such an effort is started relatively soon, the Panel believes that the information generated by such a committee would provide timely input into the next iteration of the Tables Report, approximately four years from now.

E. Conclusion

The Science Panel concludes that the final Report represents a significant contribution to increased understanding of the causal relationships between dose from ionizing radiation and cancer. In light of current scientific information, the Report generally provides sound estimates of PC values under conditions of radiation exposure reasonably analogous to those under which the data used in generating the pertinent table entries were derived. From the standpoint of their possible use, the Tables may be most valuable in extreme cases where it can be reliably inferred that a particular cancer is either highly likely, or unlikely, to have been caused by a given dose of radiation. In the intermediate range, more careful examination of specific circumstances and uncertainties may be required, but the Tables can still serve an important function by supplying an authoritative, expert estimate of the PC and the associated uncertainty based on current knowledge.

Date of review — May 24, 1985
Date of submission — June 1, 1985

Marvin Rosenstein for

Randall S. Caswell, Ph.D.
Chairman
Science Panel, CIRRPC

Lawrence B. Hobson

Lawrence B. Hobson, M.D , Ph.D.
Executive Secretary
Science Panel, CIRRPC

References

1. Science Subpanel on Radioepidemiological Tables, Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables: 1985, National Institutes of Health, Bethesda, MD 20205.

III. Science Panel Report No. 2

A. Purpose of the Review

To evaluate the draft report with respect to the scientific considerations underlying the establishment of "radioepidemiological tables" to be used to determine the probability that given cancers occurring in people with previous radiation exposure have been caused by such exposure.

B. Documents and Presentations Reviewed

"Draft Report of the Ad Hoc Working Group to Develop Radioepidemiological Tables," July, 1984

"Draft Report of the Ad Hoc Working Group to Develop Radioepidemiological Tables," September, 1984

Warren K. Sinclair: "Draft Report of the Ad Hoc Working Group to Develop Radioepidemiological Tables, September, 1984. General and Detailed Comments," October 6, 1984

Verbal Presentations by:

J. Edward Rall, Deputy Director for Intramural Research, National Institutes of Health, and Chairman, Ad Hoc Working Group

Seymour Jablon, Advisory Committee of the Radiation Effects Research Foundation, NAS-NRC, and member of the Ad Hoc Working Group

Charles O. Land, Health Statistician, Environmental Epidemiology, National Cancer Institute and member of the Ad Hoc Working Group

Warren K. Sinclair, President, National Council on Radiation Protection and Measurements

Oddvar F. Nygaard, National Cancer Institute and Case-Western Reserve University

C. Summary and Background of Reviewed Material

A summary of the current Draft Report of the Ad Hoc Working Group to Develop Radioepidemiological Tables was prepared by the Executive Secretariat, CIRRPC, and was sent to the members of this Committee separately.

Section 7, subsection b, of Public Law 97-414 (The "Orphan Drug Act") directs the Secretary of Health and Human Services (HHS), within one year after the date of enactment of this Act (January 4, 1983) to

> . . . devise and publish radioepidemiological tables that estimate the likelihood that persons with any radiation related cancer who received specific radiation doses before the onset of the cancer developed the disease as a result of such exposure. These tables shall show a probability of causation of developing each radiation related cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to the onset of the cancer in question and such other categories as the Secretary, after consulting with appropriate scientific experts, determines to be relevant.

The Secretary was also instructed to publish, with the tables, "an evaluation which will assess the credibility, validity and degree of certainty associated with such tables," and a compilation of the formulas used to calculate the probabilities of causation ("PC") tables. The tables were to be updated at least every four years in order to "insure that they continue to represent the best available scientific data and expertise."

The statement by the President, on the occasion of his signing the Orphan Drug Act, expresses the Administrations's reservations in regard to the preparation of the tables:

> . . . there is as yet no consensus among radiation experts in relating human cancers and exposure to low levels of radiation. Yet, Section 7 mandates that probability of causation tables be calculated for even very small dose levels. Accordingly, I am directing the Secretary of Health and Human Services to complete the tables to the extent that may be possible and scientifically responsible, in light of the analysis also mandated by Section 7, which requires him to 'assess the credibility, validity and degree of uncertainty associated with such tables.'

The review of the Science Panel, reported herein, is based upon reviews of the July 1984 and September 1984 draft reports of the Ad Hoc Working Group. In addition, the Science Panel has benefited from discussions of the Draft Report presented by Drs. J. Edward Rall, Charles E. Land, Oddvar F. Nygaard, Seymour Jablon and Warren K. Sinclair. The Science Panel also has maintained limited informal contact with members of the Ad Hoc Working Group in order that

each organization be aware of the deliberations of the other. Nevertheless, this review is based upon the September 1984 draft report of the Working Group and has been prepared from the perspective expressed in the President's directive.

D. Observations of the Science Panel

The Panel would like to acknowledge the excellence of the Working Group's efforts, not only in summarizing and discussing the current knowledge with respect to radiation carcinogenesis in man and in applying this knowledge in the preparation of "radioepidemiological tables," but also in advancing our insight into the time- and dose-response patterns of cancers such as leukemia and cancer of the breast, using the latest information available.

Some aspects of the Working Group's report, however, require attention in order to better define its limitations. The Panel would like to comment specificially on the following points:

- The treatment of uncertainties;
- Use of Quality Factors;
- Use of the tables for exposures resulting from internally deposited radionuclides; and
- Items requiring clarification.

E. Treatment of Uncertainties

The Working Group, in preparing the successive drafts of its report, has given increasing and well-deserved attention to the various uncertainties that affect the calculation of "probabilities of causation" (PCs). At the same time, the discussion of these uncertainties has become dispersed throughout the report. Since it is essential that the users of the tables appreciate the limitations inherent in the determination of PC, a summary of the most important uncertainties and their import for the use of PCs should be included in the preface of the report. If an Executive Summary is to be prepared, the same discussion of uncertainties should be included. Statements such as: ". . . the tables can be regarded as no more than a guide to causation in the particular case" (p. 108) and "The tables cannot now provide precise measures of the probability that certain cancers result from previous exposure" (p. 139) are important and should be emphasized from the outset.

The Working Group, to the extent that this is scientifically feasible, should better quantify the uncertainties numerically or, at least, provide expert opinion with regard to their likely magnitude. The general uncertainty at low doses was recognized by the "BEIR-III Committee" when it stated that "The Committee does not know whether dose rates of gamma or x-rays of about 100 mrads/yr are detrimental to man."[1] Because of this uncertainty, the BEIR-III lifetime risks of cancer mortality for low-LET radiation were estimated for a single whole-body dose of 10 rads and for continuous lifetime exposure of 1 rad/yr. Since the Ad Hoc Working Group uses these risk coefficients in calculating PCs, discussion of the uncertainties associated with PCs at lower doses should be presented quantified rather than merely described.

With respect to particular sources of uncertainties, the Panel feels that the influence of other carcinogens and the particular uncertainties related to low level exposures to ionizing radiation need to be summarized at the beginning of the report as well.

In summary, the Panel finds that the treatment of uncertainties should be expanded. In addition, a statement of the major uncertainties and an estimate of their magnitude should be made in the Introduction and Executive Summary

F. Use of Quality Factors

Most of the tables in the report deal with the commonly occurring low-LET radiation. In order to use the low-LET table for high-LET radiations, "quality factors" might be used. This approach implies that absorbed doses can be converted to biologically equivalent doses by multiplication by the quality factors which are used in radiation protection. These are likely to be conservative estimates of relative biological effectiveness (RBE). In addition, the quality factors may vary with dose and, therefore, use of a single factor might be inappropriate.

The Working Group is encouraged to examine, for each of the cancer types considered and for all classes of radiation, the most appropriate value of RBE to be used. Until RBEs are defined for each type of cancer and for each class of radiation, the Panel would prefer that the tables be used only for situations that have some reasonable commonality in radiation type and exposure conditions with those on which the derivation of PCs is based or, as an alternative, be employed in situations where a biologically equivalent dose for the specific cancer of interest can be determined.

In the case of lung cancer from radon progeny exposures, the Working Group should assess the

literature and express the radiation risk coefficients in terms of Working-Level Months (WLM) rather than use a dose model that requires assumptions about RBE.

G. PCs and Internally Deposited Radionuclides

The Working Group based most of the PCs on information concerning external exposures of relatively short duration. It did not examine the extensive data base on exposures from internal emitters and the induction of cancer resulting from these exposures, with the sole exceptions of Ra-224 induced bone cancer and radon induced lung cancer. Consequently, the reader of the report receives no guidance as to how to apply the methods recommended by the Working Group for external exposures to internally deposited radionuclides such as Sr-90, Ra-226 and Pu-239. In view of the fact that radiation injury may result from exposure to internally deposited radionuclides, this matter requires greater attention. Accordingly, the Panel recommends that the Working Group discuss the applicability of the tables to internal exposure situations other than those evaluated in the report.

H. Items Requiring Clarification

1. Dose-response models

The draft report, by choosing a relative risk model to describe the relationship between exposure and cancer incidence, and by assuming a multiplicative interaction between radiation and other carcinogenic risk factors, may overestimate or underestimate the PCs in cases where the interaction between radiation and other carcinogens is actually additive. The Working Group did make an exception for smoking when it calculated the PCs for lung cancer in smokers and nonsmokers. Although the Panel does not oppose the (necessarily arbitrary) decision to assume a multiplicative interaction, it recommends that the report discuss the degree of variability associated with the PCs arising from this assumption.

In the calculation of the PCs, use is made of a factor, K, which is defined as the excess incidence of cancer due to radiation divided by the baseline incidence of cancer, within a certain time span, usually 11 to 30 years after the age at exposure. The discussion in the draft report concerning the derivation of this factor needs to be improved. In addition, the consequences of using this factor in the calculation of PCs beyond a 30-year observation period needs to be assessed.

2. Inappropriateness of "prospective" PCs

The Working Group notes that PCs can be calculated prospectively, i.e., before the appearance of cancer, and that such a calculated PC "would have little meaning to any person because of its specificity" (p. 68). Nevertheless, it is quite likely that PCs will be used in this way. The Panel recommends that the Working Group expand its discussion of the inappropriateness of calculating prospective PCs and emphasize strongly its discouragement of such use. This point should be highlighted in the Preface

3. Definition of dose

The Panel feels that expanded coverage ought to be given to the definition of "dose." This is especially important if PCs are to be applied to exposure situations involving internally deposited radionuclides, even in the two limited cases discussed in the report. The Panel recommends that a general discussion be included in Chapter III, which identifies factors such as cells at risk, their mass, relationship to the source of radiation, etc., and that each section covering a particular cancer has a short summary of dose factors to be evaluated before applying PC calculations. In addition, the report should emphasize that the tables are based on organ doses and that external exposures measured on the surface of the body must be adjusted accordingly.

4. Tables vs. Formulas

The Working Group's report indicates that tables of PCs will be provided for certain ages of exposure and for exposure levels of 1, 10 and 100 rads The PC for other exposure situations is to be computed based on tables of coefficients and formulas presented in the report. The Panel agrees that it is appropriate to limit the number of tables of PCs to that necessary for illustrative purposes. The Panel considers the tables of coefficients and formulas clean and simple to use in calculating PCs

I. Conclusions

The Science Panel finds that the report of the Ad Hoc Working Group is an excellent and scientifically responsible document which provides probabilities

of causation on the basis of the current knowledge on radiation carcinogenesis in man. The Panel believes, however, that there are several aspects of the report that require attention to define more clearly the limitations of the tables. An improved discussion of the uncertainties inherent to the PC calculation and guidance concerning application of the radio-epidemiology tables to high-LET radiations and internally deposited radionuclides are particularly important. To the extent that the Panel's concerns cannot be adequately addressed by the present Ad Hoc Working Group, it is suggested that they be considered by any future Working Group established to update the tables.

Date of review — October 26, 1984
Date of submission — November 6, 1984

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1. Committee on the Biological Effects of Ionizing Radiations, *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980*, National Academy Press, Washington, D.C., 1980.

Science Subpanel on Radioepidemiological Tables

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