



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-RAC-LTR-93-004

December 9, 1992

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

OFFICE OF
THE ADMINISTRATOR

Re: Evaluation of EPA's Proposed Methodology for Estimating Radiogenic
Cancer Risks

Dear Mr. Reilly:

In a memorandum dated January 13, 1992, Margo T. Oge, Director, Office of Radiation Programs, asked the Science Advisory Board to review EPA's revised methodology for estimating human cancer risks from exposures to ionizing radiation. The charge for this review requested the SAB to respond to the following four questions:

1. Has the Agency analysis considered the most relevant risk estimates of low-LET radiation?¹
2. Does the Agency analysis accurately compare the most relevant features and assumptions of the various models?
3. Is the Agency's analysis technically sound?
4. Are the recommended methods for estimating the cancer risks appropriate and supportable in light of the current scientific evidence?

In addition to the charge, the ORP initially provided the SAB with extensive background material as listed in Appendix 1. On May 1, 1992, ORP provided the SAB with a follow-up document titled "Proposed Methodology for Estimating Radiogenic Cancer Risk."

¹ LET = Linear energy transfer, a measure of the rate at which radiations deposit energy in matter and create ionization. Gamma and beta radiation are considered to be low-LET radiation, while alpha radiation is high-LET and leads to more densely distributed ionization along its track. Adjustments must be made to make a dose of high-LET radiation biologically "equivalent" to a larger dose of low-LET radiation, by the introduction of a "quality factor" (Q) which represents an approximated average "Relative Biological Effectiveness" (RBE) factor in the low dose range.

In the opinion of the Radiation Advisory Committee EPA has reviewed and considered all major new data sets and current risk estimates of low-LET ionizing radiation. Although no single data set and model for predicting radiogenic cancer risk is ideal, the method of analysis chosen by EPA is adequately supported by present scientific evidence. A few areas of uncertainty exist that eventually may require modification of the Agency's analysis when further data become available. Among these is the method for utilizing ("transporting") risk estimates from the atomic bomb survivor study in Japan where the base-line risks for several cancers differ significantly from those in the U.S. Another is the question of whether to apply a "Dose Rate Effectiveness Factor" (DREF) for solid tumors at low dose rates or at low doses of low-LET radiation; the Agency's choice of a DREF of 2 is in accord with the current choice of other radiation protection groups world-wide. An additional concern is the continuing uncertainty in the dosimetry for the Japanese atomic bomb survivors including the magnitudes of the neutron components. Further discussion of these and other issues is contained in the subsequent parts of this Letter Report.

The Radiation Advisory Committee addressed the charge and the background materials at its meetings on February 12 and May 21, 1992 and approved this report August 5. At the first of these meetings, the Committee orally informed the ORP that its initial analysis was sufficient to guide further work and accepted ORP's proposal to limit further consideration to the cancer risk models developed for the Nuclear Regulatory Commission (NRC) by Ethel Gilbert and for the International Commission on Radiological Protection (ICRP) by Charles Land and Warren Sinclair.

On May 21, 1992, ORP described the procedure and risk coefficients² it proposed to use henceforth for estimating cancer risk from ionizing radiation. In brief, EPA proposed largely to adopt the ICRP model and use risk coefficients that are the geometric means of the two projections presented by Land and Sinclair for most cancer sites. Risk coefficients for other sites (e.g., liver, bone, and thyroid) are based on a variety of underlying data sets thought by EPA to be most appropriate. The risk coefficients presented by Land and Sinclair in ICRP Publication 60 (1991) were derived from the observations of cancers in the Japanese survivors of the atom bombs and then "transported" to the U.S. population by means of two different methods³. One method assumes that the excess relative risk in the U.S. would be the same as in Japan regardless of

² The risk coefficients are expressed as the excess probability of developing fatal cancer over a lifetime of exposure per unit dose-equivalent (rem or Sv).

³ "Transport" of radiation risk estimates across populations generally refers to the method(s) by which a cancer risk estimate obtained for one population is made applicable to (or may be compared to) that of another population when the underlying background risks for the two populations differ.

differences in baseline cancer rates (the "multiplicative" model) and the other assumes that the excess absolute risk over the period of observation will be the same in the two populations, and then projects a constant relative risk forward in time for the U.S. population (the NIH model). Both methods thus assume a constant relative risk above the baseline cancer risk in an unexposed population independent of time after exposure, except for leukemias. Furthermore, a minimum latent period of 10 years is assumed to apply for all solid tumors. The risk of radiogenic leukemia is subject to a different analysis that includes a shorter latency and a relative risk that increases with time after exposure and then declines. For cancers other than those identified by sites, EPA proposes to use the risks for exposure during ages 10-19 as an approximation of the risks for persons exposed under 10 years of age rather than the Land and Sinclair estimates. EPA's justification is that risks estimated by these authors for exposures at less than 10 years are inexplicably low for males and high for females and are based on few observations with likely high sampling errors.

With this description as background, the Committee offers the following responses to the charge:

1. Has the Agency analysis considered the most relevant risk estimates of low-LET radiation?

Yes. The Committee commends ORP for considering all the major analyses of the Japanese epidemiology as well as other studies of radiogenic cancer risks.

2. Does the Agency analysis accurately compare the most relevant features and assumptions of the various models?

For the most part, yes. ORP has presented a thorough and unbiased description of the strengths and limitations of the various data sets and analyses of radiogenic cancer risk. The Agency could have noted that several of the risk estimates presented in the NRC proposal are not directly dependent on the dosimetry in the atom bomb survivors and are therefore more robust, in a limited sense, than are the estimates in the ICRP model.

3. Is the Agency analysis technically sound?

For the most part, yes. While arguments could be raised that the National Academy of Sciences BEIR V report contains results that might have been given greater consideration, the risk estimates for all cancer sites combined are relatively consistent among all analyses of the Japanese experience, and this estimate is the one primarily needed by EPA because most regulations will be based on overall

cancer risk. The following remarks respond to four specific important aspects of the Agency's analysis: the geometric mean of transport models, dose rate effectiveness factor(s), relative biological effectiveness (RBE) for alpha radiation, and uncertainty analysis.

a) Geometric Mean of Transport Models

The Committee notes that EPA did not offer any scientific rationale for using the geometric mean rather than consistently using one or the other of the transport models or using a different weighting procedure (e.g., the arithmetic mean). The Agency did effectively argue that neither of the transport models gave results that seemed reasonable for all individual organs, and supported the idea that the geometric mean for each organ provides a measure of central tendency that reflects the results of each of the models without allowing the result of one to dominate the mean value. At the same time, the geometric mean seems the more consistent with the limited data available on the radiogenic cancer risks in the U.S. The risks thus calculated are also reasonably consistent with the NRC risk coefficients, which were derived judgmentally from both the Japanese data transported to the U.S. and other considerations. Thus the EPA procedure is as supportable as any other for estimating organ-specific and total cancer risks from low-LET radiation. The Committee notes, however, that the site-specific risk estimates are far from firm and should be used with caution; it is likely that the diagnosis of cancer in the Japanese was significantly in error for some sites, particularly in earlier years. This limitation was one of the reasons why the NAS BEIR V committee provided risk estimates for certain organ systems but not for individual organs within those systems. While the Committee recognizes the necessity to make organ-specific risk estimates for situations involving internally deposited radionuclides that are not distributed uniformly in the body, the Agency's documentation should make it clear that there are relatively larger uncertainties for organ-specific risk estimates than for the estimated whole-body radiation risks.

b) Dose Rate Effectiveness Factor(s)

The overwhelming majority of studies with both experimental animals and with cells in culture have shown that in terms of lethality, mutagenesis, and tumorigenesis, a given dose of low-LET radiation is significantly more effective when administered at a high dose rate than when administered at a low dose rate or when administered as multiple small fractions over a longer period. This observation is incorporated in most current radiation risk estimation procedures through use of a Dose Rate Effectiveness Factor (DREF). Most DREFs determined in experimental systems fall in the range 2 to 10 (NCRP report 64).

Epidemiological studies have not produced data in support of a DREF for carcinogenesis in humans except in the case of leukemia, for which the dose-response is best described by a "linear-quadratic" model that in itself produces a DREF because the quadratic term becomes insignificant at low doses and at low dose rates of low-LET radiation. The dose-response relationships for solid tumors are best described by a linear model; it should be kept in mind, however, that excess cancer risks at low radiation doses (e.g., less than 0.10 Gy) are generally too small to be observed directly.

EPA has proposed to use a DREF of 2 for radiation-induced solid tumors; that is, EPA will assume that low-LET radiation accrued at high doses and dose rates (e.g., in the Japanese atomic bomb studies) is twice as likely to cause cancer as the same dose accrued at low dose rates. The Committee agrees that this choice is reasonable; it is consistent with current scientific judgment, and it is in the lower range of DREFs observed in experimental systems.

EPA questions whether it should use a DREF of 1 (i.e., no dose rate adjustment) for the observed risks of radiogenic breast cancer and thyroid cancer, arguing that dose fractionation did not show much reduction in risk for breast cancer in women exposed to repeated fluoroscopic x-rays. The Committee believes that this observation does not rule out a dose-rate effect, because each fraction was delivered at a high dose rate; it is not aware of any good data set for induction of human breast cancer at low dose rates. Similarly, the data on thyroid cancer do not include exposures at truly low dose rates. Thus, the breast and thyroid need not be treated differently from other organs with respect to their response to low dose rates. Some scientists believe that it is more parsimonious to argue for a DREF of 1 in humans lacking epidemiologic evidence for a dose rate effect. It should be noted that a DREF of 1.0 (i.e., the absence of a dose rate effect) represents the more conservative approach to low-dose and low dose-rate risk estimation which might be viewed as a more prudent stance for a regulatory agency in setting radiation protection standards. However, the Committee is not prepared to reject a DREF of 2 or greater in all tissues, whether animal or human, in view of the considerable evidence for a dose rate effect in experimental systems. Also, by applying a DREF of 2 for most if not all organ-specific risk estimates, EPA will be in harmony with other radiation protection groups worldwide.

The Committee recognizes the potentially large policy implications of the choice and application of a DREF since the great majority of environmental and occupational low-LET radiation exposures will occur at low dose rates. If the Agency decides to apply a DREF, the Committee strongly suggests that EPA define a boundary between low and high dose rates so that users of EPA risk

coefficients will not inadvertently apply a DREF in situations for which it is inappropriate.⁴

c) Relative Biological Effectiveness (RBE) for Alpha Radiation

As EPA points out, the Relative Biological Effectiveness (RBE) to be used for alpha radiation depends on the choice made for the DREF for low-LET radiation, because alpha radiation risks per unit dose do not appear to vary significantly with dose rate. Sufficient direct epidemiological data are available to estimate the risk per unit exposure of high-LET alpha-particle-emitting radionuclides for both leukemias and respiratory cancer. Hence, for the most common cancers related to alpha-particle irradiation, no need exists to use low-LET risk coefficients in combination with an RBE or Q factor (see footnote 1). The Committee commends EPA for proposing to use high-LET risk information directly (e.g., for the risks of exposures to radium and radon).

Where direct epidemiological data are not available to support such risk estimation procedures, the Committee agrees that an RBE of 20 be used for alpha radiation in conjunction with a DREF of 2 for low dose rates of low-LET radiation. When comparing risk of alpha-particle radiation with risk from acute, high-dose low-LET radiation, however, an RBE of 10 should be used.

Although not commonly required for EPA risk estimation tasks, it may be useful for the Agency to provide a Q factor for neutron radiation, if only to assure that the use of the Japanese epidemiology in the development of its risk coefficients remains valid in the event of further adjustments to the atomic bomb dosimetry (see below).

d) Uncertainty Analysis

The Committee is gratified by EPA's intent to estimate the cumulative uncertainties in its calculated risk coefficients. This undertaking is crucial to informed use of the risk estimates.

The uncertainty analysis should include the uncertainty in the dosimetry for the Japanese atom bomb survivors which for individual doses could be as great as 30-45%. Furthermore, the whole set of dose estimates might be biased towards the low side because the 1986 dosimetry may have discounted the neutron

⁴ In the case of low-LET radiation, NCRP Report No. 64 suggested upper boundaries for low dose of 20 rad (0.2 Gy) and for low dose rate 5 rad (0.05 Gy) per year. EPA may decide to select other boundaries.

component too much. A small increase in neutron doses would produce a larger increase in dose equivalents (physical doses x Q factor) and reduce the risk estimates for low-LET radiation correspondingly. Moreover, uncertainty analyses should be conducted for the risk estimates for individual organs which, as pointed out above, are much less robust than the risk estimate for total cancers.

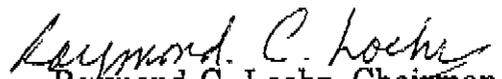
In assigning an uncertainty to the DREF, the Committee recommends that EPA also consider observations that the DREF might be larger than 2 as well as those suggesting it might be as small as 1.

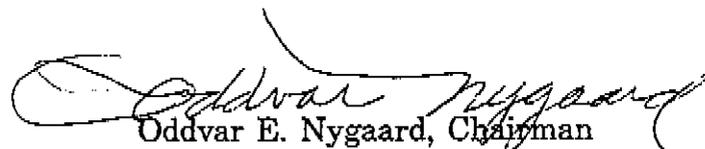
4. Are the recommended methods for estimating the cancer risks appropriate and supportable in light of the current scientific evidence?

Yes, with the cautions noted in the response to Question 3, above. The Committee commends the Agency for its preparation of material to support its proposed methodology and notes that the subject is not easy to cover in a few pages of text.

The Science Advisory Board appreciates the opportunity to comment on Agency's proposed methodology for estimating radiogenic cancer risks and looks forward to receiving a summary of EPA's responses to the comments provide above.

Sincerely,


Raymond C. Loehr, Chairman
Executive Committee
Science Advisory Board


Oddvar E. Nygaard, Chairman
Radiation Advisory Committee
Science Advisory Board

Enclosures: Committee Roster
Appendix I: List of Background Material Provided by the
Office of Radiation Programs

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APPENDIX I
Background Material Provided by the
Office of Radiation Programs

1. "Reevaluation of EPA's Methodology for Estimating Radiogenic Cancer Risks", background document presented to RAC in January 1992.
2. "Proposed Methodology for Estimating Radiogenic Cancer Risk", background document presented to the RAC in May 1992.
3. Portions of 1990 Recommendations of the International Commission on Radiological Protection, ICRP Publication 60. Ann. ICRP 21, 1991.
4. Land, C.E. and W.K. Sinclair, "The Relative Contributions of Different Organ Sites to the Total Cancer Mortality Associated with Low-Dose Radiation Exposure" Ann. ICRP 22, 1991.
5. "Health Effects Models Developed from the 1988 UNSCEAR Report", NRPB-R226.
6. Gilbert, E.S., in Health Effects Models for Nuclear Power Accident Consequence Analysis, NUREG/CR-4214, Rev. 1, Part II, Addendum 1, Chapter 3, LMF-132.

U.S. ENVIRONMENTAL PROTECTION AGENCY

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ABSTRACT

In a memorandum dated January 13, 1992, Margo T. Oge, Director, Office of Radiation Programs, asked the Science Advisory Board to review EPA's revised methodology for estimating human cancer risks from exposures to ionizing radiation. The charge for this review requested the SAB to respond to the following four questions:

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KEYWORDS: Radiation Risk Assessment, Low-LET, Radiogenic Cancer Risk

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