United States Environmental Protection Agency
Science Advisory Board Washington, DC
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AN SAB REPORT: ESTIMATING UNCERTAINTIES IN RADIOGENIC CANCER RISK

REVIEW OF THE OFFICE OF RADIATION AND INDOOR AIR'S DRAFT DOCUMENT *ESTIMATING RADIOGENIC CANCER RISKS DRAFT ADDENDUM: UNCERTAINTY ANALYSIS* BY THE RADIATION ADVISORY COMMITTEE

February 18, 1999

EPA-SAB-RAC-99-008

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Re: Review of the Office of Radiation and Indoor Air October, 1997 Draft Document *Estimating Radiogenic Cancer Risks Draft Addendum: Uncertainty Analysis* (October, 1997)

Dear Ms. Browner:

In 1994, EPA published *Estimating Cancer Risks*, describing the Agency's methodology for calculating excess cancer morbidity and mortality risks due to ionizing radiation. Subsequently, the risk projections of EPA's 1994 document were updated and extended in light of more recent U.S. vital statistics provided in EPA's 1998 Federal Guidance Report, Number 13 (FGR 13).

The present EPA methodology provides quantitative estimates of uncertainty in cancer mortality per gray (Gy) of radiation absorbed dose delivered at low doses and low dose rates by both low-Linear Energy Transfer (LET) and high-LET radiation to the whole body, the lungs, and the bone marrow. The risk of radiogenic cancer incidence is based on the quotient of the risk of a radiogenic mortality and a lethality fraction.

The Science Advisory Board (SAB) was asked to by the Office of Radiation and Indoor Air (ORIA) to review the EPA draft document of October 1997 entitled *"Estimating Radiogenic Cancer Risks Draft Addendum: Uncertainty Analysis,"* which presented the methodology developed by EPA to estimate uncertainty in its projections of radiogenic cancer risk. The Uncertainty in Radiogenic Cancer Risk Subcommittee (URRS) of the SAB's Radiation Advisory Committee (RAC) subsequently convened in public meetings in Washington DC, on November 20, 1997 and March 4, 1998 to receive briefings from the ORIA and interested members of the public, and to discuss the relevant issues.

In its Charge to the SAB, EPA asked three questions:

a) Are the relevant sources of uncertainty addressed?

b) Is the overall approach to quantifying and combining uncertainties appropriate?

c) Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?

One additional issue identified during the public meeting, was also addressed: the possibility of “unknown” sources of uncertainty in addition to the seven identified by EPA.

Overall, the Subcommittee believes that EPA has generated a credible document, using published techniques in identifying and combining the various sources of uncertainty. We applaud EPA for recognizing the importance of describing the state of knowledge of uncertain input variables as subjective probability distributions and using Monte Carlo simulation to combine these input uncertainties into a subjective probability distribution of radiogenic cancer risk. We note that in other offices of EPA, the application of this approach to the evaluation of the dose response of specific contaminants is still a subject of internal discussion. In issuing its October 1997 Draft Addendum, the ORIA is demonstrating a leadership position within the Agency. We encourage the EPA to build on the draft methodology and issue a single, integrated document that clearly describes the EPA’s methodology for estimation of specific cancer incidence and mortality risks per unit intake of radioactivity, along with their associated uncertainty. This would be an extension of the work initiated in FGR 13..

As with examining any such complex undertaking, our review found areas in which improvement was possible. These areas, and our recommendations are:

a) The primary data used for risk estimation should be the Radiation Effects Research Foundation 1992 data on cancer incidence rather than on cancer mortality.

(1) Data on cancer incidence are affected less by cancer misclassification than are data based on mortality.

(2) Use of data based on cancer incidence avoids the uncertainty introduced when applying lethality fractions to data on cancer mortality.

(3) Lethality fractions may vary greatly across populations and time, and may represent an additional source of uncertainty (which EPA's present approach appears to underestimate).

b) The subjective probability distribution for extrapolation from high to low dose rates for low-LET radiation should include a greater weight for the possibility that the low Dose and Dose Rate Effectiveness Factor (DDREF) could be less than or equal to 1.0, as well as for values higher than 5.0. In any case, EPA should provide stronger justification to explain why a subjective weight is not given for values exceeding 5.0. The values chosen for the DDREF could also vary depending on the type of cancer and organ affected.

c) EPA should consider the additive, multiplicative, and National Institutes of Health (NIH) models as alternative modeling approaches for transferring radiogenic cancer risk from the Japanese Lifespan Survival Study cohort to the U.S. population. EPA should assign a subjective weight to each model (additive, multiplicative, and NIH), rather than using a coefficient based on the geometric mean of the latter two model results.

d) EPA has multiplied the probabilities of uncertain input variables to obtain a joint probability of the radiogenic cancer risk. This multiplication has been performed assuming statistical independence among these quantities. This assumption may be incorrect. For example, statistical sampling errors in the epidemiological follow-up of exposed cohorts can be affected by diagnostic misclassification of cancer mortalities; thus, a dependency between these two variables does exist. Further investigation should explicitly consider the effect of dependencies among the inputs used to estimate the radiogenic cancer risk.

e) For those inputs that dominate the overall uncertainty in radiogenic cancer risk, use of more formal methods of expert elicitation would be desirable to obtain defensible estimates of subjective distributions that reflect the current state of knowledge. Formal elicitation of expert judgment would be preferred to informal estimates made by EPA staff. Currently, the subjective probability distributions specified by EPA staff

reflect only the state of knowledge of the EPA. A more formal elicitation would encompass an evaluation of extant data sets by a broader spectrum of expertise both inside and outside of EPA.

f) As additional information becomes available, the currently specified subjective probability distributions should be updated objectively using an intellectually consistent approach (such as a Bayesian process) to reflect improvements in the state of knowledge. Opportunities for updating should be encouraged, and incentives provided, when uncertainty levels are too high to permit confident decision making.

The RAC and its Subcommittee appreciate the opportunity to provide this report to you and we hope that it will be helpful. We look forward to the response of the Assistant Administrator for the Office of Air and Radiation to this report in general and to the comments and recommendations in this letter in particular.

Sincerely,

/signed/
Dr. Joan M. Daisey, Chair
Science Advisory Board

/signed/
Dr. Stephen L. Brown, Chair
Radiation Advisory Committee
Science Advisory Board

/signed/
Dr. F. Owen Hoffman, Chair
Uncertainty in Radiogenic Risk Subcommittee
Radiation Advisory Committee

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ABSTRACT

The Science Advisory Board (SAB) was asked by EPA's Office of Radiation and Indoor Air (ORIA) to review the 1997 draft document entitled *"Estimating Radiogenic Cancer Risks Draft Addendum: Uncertainty Analysis,"* October, 1997. The Charge to the SAB focused on evaluating sources of uncertainty, methods of quantifying uncertainties, and the mathematical quantification of sources of uncertainty.

The review of the Uncertainty in Radiogenic Risk Subcommittee (URRS) of the SAB has concluded that EPA has generated a credible document. The state of knowledge of uncertain input variables has been properly described by the Agency staff within the Office of Radiation and Indoor Air (ORIA) as subjective probability distributions. Monte Carlo simulation is properly employed to combine these input uncertainties into a subjective probability distribution of radiogenic cancer risk. EPA is encouraged to build on the draft methodology and issue a single document that clearly describes its methodology for estimating specific cancer-incidence and mortality risks per unit intake of radioactivity, along with their associated uncertainty.

URRS recommendations for improving the draft report include (a) use of primary data based on cancer morbidity rather than mortality; (b) expansion of the subjective probability distribution for extrapolating from high to low dose and dose rates; (c) accounting explicitly for alternative modeling approaches used to transfer risk coefficients from data on the survivors of the atomic bombings of Japan to estimated risks in the U.S. population; and (d) the use of formal methods of expert elicitation to quantify uncertainty for the most important input variables, so that subjective probability distributions reflect the current state of knowledge.

KEYWORDS: uncertainty; radiogenic risk of cancer; subjective probability.

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1 Participated in review of document, but was unable to attend face-to-face public meetings.

2 Subject matter expert.

3 Provided editorial support for preparation of this report, but did not participate in the review.

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[4] Declined to participate in review.

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1 EXECUTIVE SUMMARY

In 1994, EPA published *Estimating Cancer Risks* (EPA, 1994), which described the Agency's methodology for calculating excess cancer morbidity and mortality risks due to ionizing radiation. Subsequently, the risk projections of the 1994 report were updated in light of more recent U.S. vital statistics which were used to complete EPA's 1998 Federal Guidance Report No. 13 (FGR 13). The most recent attempt by EPA to quantify the uncertainty in its risk estimates was provided to the SAB as a draft document "*Estimated Radiogenic Cancer Risks Draft Addendum: Uncertainty Analysis"* (EPA, !997).

The present EPA methodology provides quantitative estimates of uncertainty in cancer mortality per gray (Gy) of absorbed dose delivered at low doses and low dose rates by both low linear-energy-transfer (LET) and high-LET radiation to the whole body, the lungs, and the bone marrow. A risk of radiogenic cancer incidence is based on the quotient of the risk of a radiogenic mortality and a lethality fraction (obtained from cancer survival statistics).

The EPA methodology includes seven sources of uncertainty:

a) statistical sampling errors of cancer mortality in the survivors of the atomic bombings of Hiroshima and Nagasaki, as indicated by the Lifespan Survivor Study (LSS) data,

b) diagnostic misclassification of cancer mortalities in the LSS cohort,

c) projection of risk in the LSS cohort out to the entire lifetime for all exposed individuals in that cohort,

d) transfer of risk estimates determined from the LSS data to the US population,

e) errors in dose estimates made for the LSS cohort,

f) extrapolation of risk from high dose rates of low-LET radiation received by the LSS cohort to low dose rates expected for populations receiving chronic exposures to man-made and natural radionuclides in the environment, and

g) the difference in the relative biological effectiveness (RBE) between high-LET radiation (i.e., alpha particles) and low-LET radiation.

EPA's 1997 document represents each of the first six sources of uncertainty as a series of bias correction factors that in turn are multiplied by the nominal risk values used in the earlier report (EPA, 1994) that described EPA's methodology for estimating radiogenic cancer risks. For a uniform, whole- body, low dose-rate exposure, that nominal value is 5.75 X 10^{-2} fatal cancers[5] per Gy. This value is intended to represent the risk to a member of the population who can be defined as an average of relevant characteristics, e.g., gender and age.

The uncertainty in the bias correction factors is described by subjective probability distributions representing EPA's current state of knowledge. Some of the information documenting the need for a bias correction has recently been published in Federal Guidance Report No. 13 (EPA, 1998). The general approach used by EPA (1997) to quantify uncertainty is similar, but not entirely identical, to the recent report No. 126 by the National Council on Radiation Protection and Measurements (NCRP, 1997). The combining of subjective probability distributions for uncertain inputs to obtain a subjective probability distribution for the excess lifetime risk per gray (Gy) from whole-body radiation is performed using Monte Carlo simulation. The approach is similar to that emphasized in NCRP Report 126 (NCRP, 1997) and consistent with the recommendation in NCRP Commentary No. 14 (NCRP, 1996). Both of these latter reports were commissioned by EPA.

In the October 1997 Draft Addendum, EPA summarizes the uncertainty in radiogenic cancer risk upper and lower limits (for 90% subjective confidence intervals) ranging from 1.0 to 10 X 10^{-2} Gy^{-1} for whole-body radiation, from 0.19 to 2.0 X 10^{2} Gy^{-1} for the lungs, and from 0.15 to 0.8 X 10^{2} Gy^{-1} for leukemia.

The Uncertainty in Radiogenic(Cancer) Risk Subcommittee (URRS) of the SAB's Radiation Advisory Committee subsequently convened public meetings in Washington DC, on November 20, 1997 and March 4, 1998 to receive briefings from the Office and Radiation and Indoor Air (ORIA) and other interested members of the public, and to discuss the relevant issues identified in the Charge (The detailed Charge is provided in Section 2.2 of this report, below).

In its review of the EPA October 1997 Draft Addendum, the Subcommittee found a need for improvement in the following areas:

a) The primary data used for risk estimation should be the Radiation Effects Research Foundation (RERF) data on cancer incidence rather than cancer mortality.

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[5] Updated in the current (1997) EPA report from 5.09 X 10^{-2}

(1) Data on cancer incidence are affected less by cancer misclassification than are data based on mortality.

(2) Use of data based on cancer incidence avoids the uncertainty introduced when attempting to estimate cancer incidence rates from cancer mortality data.

(3) Lethality fractions may vary greatly across populations and time and may represent an additional source of uncertainty which EPA's present approach appears to underestimate.

b) The subjective probability distribution for extrapolation from high to low doses and dose rates for low-LET radiation should include a greater weight for the possibility that the low Dose and Dose Rate Effectiveness Factor (DDREF) could be less than or equal to 1.0, as well as for values higher than 5.0. In any case, EPA should provide stronger justification to explain why a subjective weight is not given for values exceeding 5.0. The values chosen for the DDREF could also vary depending on the type of cancer and organ affected.

c) EPA should consider the additive, multiplicative, and National Institutes of Health (NIH) models as alternative modeling approaches for transferring radiogenic cancer risk coefficients from the LSS cohort to the U.S. population. EPA should assign a subjective weight to each model (additive, multiplicative, and NIH), rather than using a coefficient based on the geometric mean of the latter two model results.

d) Multiplication of probabilities to obtain the joint probability is appropriate only for statistically independent quantities. Possible dependence of the quantities multiplied together should be investigated. For example, statistical sampling errors can also be affected by diagnostic misclassification of cancer mortalities.

e) For those inputs that dominate the overall uncertainty in radiogenic cancer risk, use of more formal methods of expert elicitation would be desirable to obtain defensible estimates of subjective distributions that reflect the current state of knowledge. Formal elicitation of expert judgment would be preferred to informal estimates made by EPA staff. Currently, the subjective probability distributions specified by EPA staff reflect only the state of knowledge of the EPA. A more formal elicitation would encompass an evaluation of extant data sets by a broader spectrum of expertise both inside and outside of EPA.

f) As additional information becomes available, the currently specified subjective probability distributions should be updated objectively, using an intellectually consistent process such as Bayesian updating to reflect improvements in the state of knowledge. Opportunities for updating should be encouraged, and incentives provided, when uncertainty levels are too high to permit confident decision making.

Overall, we believe that EPA's Office of Radiation and Indoor Air (ORIA) has documented a credible methodology using published techniques to identify and combine the various sources of uncertainty. We applaud EPA for recognizing the importance of describing the state of knowledge of uncertain input variables as subjective probability distributions and using Monte Carlo simulation to combine these input uncertainties into a subjective probability distribution of radiogenic cancer risk. We note that in other offices of EPA, the application of this approach to the evaluation of the dose-response of specific contaminants is still a subject of internal discussion. In issuing its October 1997 Draft Addendum (EPA, 1997), EPA's ORIA is demonstrating a leadership position within the agency. We encourage the EPA to build on the 1997 draft methodology (EPA, 1997) and issue a single, integrated document that clearly describes the EPA's methodology for estimation of specific cancer incidence and mortality risks per unit intake of radioactivity, along with their associated uncertainty. This would be an extension of the work initiated in Federal Guidance Report No. 13 (EPA, 1998; See also U.S. EPA/SAB, 1998).

2 INTRODUCTION

2.1 Background

In 1994, EPA published *Estimating Cancer Risks* (EPA, 1994), which described the Agency's methodology for calculating excess cancer morbidity and mortality risks due to ionizing radiation (EPA, 1994). Subsequently, the risk projections of EPA 1994 were updated in light of more recent U.S. vital statistics (Federal Guidance Report No. 13 (EPA, 1998) and were published in the draft document *Estimating Radiogenic Cancer Risks Draft Addendum: Uncertainty Analysis* (EPA, 1997). The present EPA methodology provides quantitative estimates of uncertainty in cancer mortality per gray (Gy) of radiation dose delivered at low doses and low dose rates by both low-linear energy transfer (LET) and high-LET radiation to the whole body, the lung, and the bone marrow. A risk of radiogenic cancer incidence is based on the risk of radiogenic mortality divided by an estimate of the fraction of the population who survive after being diagnosed with cancer.

The SAB was asked to review the methodology developed by EPA to estimate uncertainty in its projections of radiogenic cancer risk (EPA, 1997) (The detailed Charge is provided in Section 2.2 of this report, below). The Uncertainty in Radiogenic (Cancer) Risk Subcommittee (URRS) of the SAB's Radiation Advisory Committee subsequently convened public meetings in Washington, DC on November 20, 1997, and on March 4, 1998, to receive briefings from the Office and Radiation and Indoor Air (ORIA) and other interested members of the public, and to discuss the relevant issues.

2.2 Specific Charge

In its charge to the SAB, EPA asked three questions:

a) Are the relevant sources of uncertainty addressed?

b) Is the overall approach to quantifying and combining uncertainties appropriate?

c) Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?

The following sections of this report address, in detail, the questions posed by the Charge for each of the sources of uncertainty. Two additional issues are also discussed: a) the possibility of "unknown" sources of uncertainty in addition to the seven identified by EPA; and b) separation of the correction of bias in nominal values from uncertainty due to lack of knowledge about true values.

3 DETAILED DISCUSSION

3.1 Review of the Primary Sources of Uncertainty

3.1.1 Statistical Sampling Errors in the LSS Data Set

EPA (1997) describes a unitless bias correction factor for statistical sampling variation in the Lifetime Survival Study (LSS) data as a normal distribution with a mean of 1.0 and a standard deviation of 0.15 for estimating the risk of low-level, low-LET, whole body radiation. For lung cancer from low-dose irradiation of the lungs, a normal distribution is assumed with a mean of 1.05 and a standard deviation of 0.29. For leukemia from low-dose irradiation of the bone marrow, EPA assumes a normal distribution with a mean of 1.05 and a standard deviation of 0.18. The Subcommittee considered the following specific issues posed by the Charge:

a) *Are the relevant sources of uncertainty addressed?*

The relevant sources are addressed, but it must be understood that a major philosophical transition has been made from statistical confidence intervals obtained from classical statistical analysis of LSS data (Shimizu *et al*., 1990) to subjective probability distributions used to extrapolate beyond the domain of direct observation, based on the state of knowledge about a dose response.

b) *Is the overall approach to quantifying and combining uncertainties appropriate?*

There is a need to make a clear distinction between classical confidence intervals (CCI) and subjective confidence intervals (SCI). Proper interpretation of the CCI shows that an unknown true value is not always contained in the CCI (Neyman, 1977). Adoption of the same numerical values from the CCI as the upper and lower bound of the SCI (as has been done in the review document (EPA, 1997)) carries a risk that the unknown true value of a parameter may lie outside of the SCI.

The calculation of the new “expectations” in the EPA (1997) report using the numerical limits of the CCI may produce upward or downward bias. This introduction of bias follows from the properties of the CCI, since CCIs will, a certain fraction of the time, lie above or below the true value.

c) *Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?*

The distributions assumed by EPA to characterize the state of knowledge for errors due to statistical sampling appear to be appropriate. It would be

preferable, however, to use previous knowledge to specify prior distributions and then update these distributions with the data given in Shimizu *et al*. (1990).

3.1.2 Diagnostic Misclassification in the LSS Data Set

EPA recognizes two types of diagnostic misclassification of cancer: classification of cancer as non-cancers (detection error), and erroneous classification of non-cancers as cancers (confirmation error). For low-level, low-LET, whole body radiation, the uncertainty in diagnostic misclassification of cancer mortality is described as an uncertain multiplicative bias correction factor (unitless) with values being normally distributed with a mean of 1.2 and a standard deviation of 0.06. For irradiation of the lungs, a mean of 1.3 and a standard deviation of 0.15 is assumed. For irradiation of the bone marrow, uncertainty is assumed to be negligible. The Subcommittee considered the following specific issues posed by the Charge:

a) Are the relevant sources of uncertainty addressed?

The relevant sources are addressed; however, uncertainty could be substantially reduced by using available data on cancer incidence rather than data on mortality (see Appendix A).

b) Is the overall approach to quantifying and combining uncertainties appropriate?

It is appropriate to state uncertainty as a subjective probability distribution of possibly true values and to use Monte Carlo procedures to combine all sources of uncertainty into an overall distribution of radiogenic cancer risk.

c) Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?

Lifetime risks of radiation-induced cancer are typically projected on the basis of mortality or incidence with the Agency choosing mortality-based data in this case. Mortality projections are determined from direct application of LSS mortality risk coefficients to baseline cancer mortality rates in other populations. However, studies in the U.S. and Japan have evaluated the use of death certificate data as the basis for calculating risk estimates and found these data to be inaccurate and of limited use

because a) mortality risks as an index of harm underestimate incidence rates; b) death certificate-based mortality risks do not reveal patterns of risk and survival by stage of cancer and histological cell type; c) death certificate-based mortality cannot include risk for benign (non-fatal) cancers; and d) death certificate-based mortality risks require an additional bias correction for diagnostic misclassification (Chao and Devesa, 1996; Gittelsohn and Senning, 1997; Hoel *et al*., 1993; Kircher *et al*., 1985; Percy *et al*., 1981; Percy *et al.*, 1990). Incidence-derived risk is projected two ways: (1) by projecting mortality risks first and then dividing results by a "lethality" fraction (deaths/new cases) to get incidence or by (2) direct application of atomic bomb survivor incidence risk coefficients to baseline cancer incidence rates in other populations. The former mortality-based incidence method is biased by both diagnostic misclassification and unknown variation in lethality fractions across time, across populations, and across cancer sites. The latter incidence method does not suffer from bias arising from use of death certificate-based information or lethality fractions.

Because projection methods involving mortality are affected adversely by the issues noted above, we have significant reservations about these sources of uncertainty which are unnecessarily introduced by EPA's effort for projecting (mortality-based) human risks of radiation-induced cancer. Given the current availability of incidence data upon which radiation protection standards could appropriately be based, it would seem reasonable to revise the goal of radiation protection to one of protecting individuals from exposures that place them at increased risk of developing cancer, rather than protecting them from exposures leading to an increased risk of dying from cancer. Further, the use of mortality as an endpoint of concern is inconsistent with most of EPA's risk carcinogen risk assessments, which are based on disease incidence. Incidence data from the LSS are available and should serve as the primary basis for EPA's estimates of radiogenic cancer risk in order to reduce uncertainty and increase credibility. The Subcommittee notes that the preceding discussion notwithstanding, moving to incidence-based projections constitutes a major policy decision, and should be considered very carefully before such an action is taken (see Appendix A for further discussion of this topic).

3.2 Temporal Projection of Risk

This source of uncertainty reflects the fact that many survivors of the bombings of Hiroshima and Nagasaki who were exposed in childhood are still alive. EPA describes the uncertainty in temporal dependence to be a unitless bias correction

factor that is multiplicative, with the assumption made in the EPA (1994) document that the relative risk is constant, but that the risk coefficients decrease with age (at time of exposure), especially for those exposed in childhood.

For cancer mortality from whole-body irradiation, a uniform distribution is assumed by EPA, with a range from 0.5 to 1.0 for the lung, breast, thyroid, and remaining sites. For the colon, a uniform distribution of 0.4 to 1.0 is assumed. For the esophagus, liver, bladder, ovaries, and skin, EPA assumes a uniform distribution ranging from 0.8 to 1.5 to reflect the fact that the data for these sites are sketchy and heavily weighted towards adult exposures.

For uniform, whole-body irradiation, the uncertainty in the temporal projections of risk for all solid tumors is described as a trapezoidal distribution with limits of 0.5 and 1.1, with most likely values ranging from 0.6 to 1.0. This distribution reflects the fact that the overall effect of temporal projection should result in the tendency to over-estimate the true risk when using the nominal risk value of 5.75×10^{-2} Gy^{-1} (EPA, 1997). For mortality due to low-dose irradiation of the lungs, it is a uniform distribution ranging from 0.5 to 1.0. For leukemia from irradiation of the bone marrow, EPA assumes a normal distribution with a mean of 1.1 and a standard deviation of 0.05. The Subcommittee's specific response to the Charge follows below.

a) Are the relevant sources of uncertainty addressed?

The relevant sources are identified, but these sources may need to be modified if data on cancer incidence are used instead of data limited to cancer mortality. It must also be made clear that EPA is only dealing with average age-at-exposure, since uncertainties in model projections of childhood exposures far exceed the uncertainty used by EPA.

b) Is the overall approach to quantifying and combining uncertainties appropriate?

For a particular outcome, lifetime risk is described by estimating the age-specific changes in excess risk as a function of time since exposure and then using this information to project patterns for age-time blocks not adequately covered by current data. As of 1985, 39% of the LSS sample survivors had died. Although some current information indicates that the relative risk (RR) is reasonably constant for both total solid cancers and leukemia, data are not yet available on the level of radiation-related cancer risk at advanced ages among people exposed at early ages. The extent to which the relative risk model applies to the LSS population exposed in childhood has been questioned by UNSCEAR (1994). For example, the increased risk for lung cancer remains elevated with the A-

bomb survivors, while with spondylitic patients treated with x-rays, there is no observed increase in risk 25 years after exposure. The proposed modifications to the constant RR model allow for a decrease with time in the non-leukemia cancer mortality for the youngest survivors.

The EPA analysis divides the cancers into three groups, by type of temporal projection used:

(1) follow-up is complete,
(2) constant relative risk with dependence on age at exposure, and
(3) constant relative risk.

No uncertainty is assigned to category (1), while the multiplicative bias correction factors (unitless) for categories (2) and (3) are assigned uniform uncertainty distributions of (0.4, 1) and (0.8, 1.5), respectively.

Leukemia is classified in EPA's group 1 with no uncertainty used on the temporal projection of risk. This assumption appears too restrictive. The effects on risk estimates of the choice of temporal projections may be as much as a factor of two as illustrated on pages 204-205 in BEIR V (NAS/NRC, 1990). Some recognition is needed of the uncertainty in the choice of method for modeling the time since exposure for leukemia.

Lung cancer is placed in EPA's group 2. BEIR V assumed that there was a decreasing relative risk with time for lung cancers. If the risk models applied do not contain this assumption, then the uniform (0.4, 1) distribution is appropriate for lung cancer, based on an average age at exposure. This distribution is quite inadequate, however, if the risk from exposure during childhood is to be calculated. For example, the lifetime risk of respiratory cancer drops from 249 to 17 for an exposure to a 5-year-old male, based on models 0 and 1 in Table 4D-6 of BEIR V, if a time-since-exposure parameter is added to either model. Therefore, the probability distribution assumed by EPA to represent uncertainty must be restricted only to risks based on average age at exposure and not to risks based on specific ages at exposure.

c) *Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?*

Changes to the subjective probability distributions specified by EPA would be warranted to reflect the additional uncertainty referred to above.

3.3 Transfer of Risk from the LSS Cohort to the U.S. Population

Uncertainty exists over how to apply the results of the analysis of the Japanese atomic bomb survivors to the estimation of risk in the U.S. population, particularly for cancer sites which exhibit markedly different baseline rates in the two populations. EPA has adopted a model for most organ sites in which the age- and sex-specific risk coefficients are a geometric mean of the corresponding coefficients used in the multiplicative and National Institutes of Health (NIH) projection models. In transferring risks across populations, the multiplicative model presumes that the excess risk (i.e., the greater risk for those exposed to acute doses, as compared to the risk for those exposed to the same dose delivered at a low dose rate) will scale with the baseline cancer rate, whereas the NIH model (NIH, 1985) presumes that the excess risk is nearly independent of differences in the baseline rate. For the risk of cancer mortality, EPA assumes an uncertain multiplicative bias correction (unitless) that is described by a normal distribution with a mean of 1.1 and a standard deviation of 0.12. For lung cancer mortality, it is a log-uniform distribution ranging from 0.5 to 2.0. For leukemia, it is a normal distribution with a mean of 1.0 and a standard deviation of 0.1. The specific issues of the Charge are addressed below:

a) Are the relevant sources of uncertainty addressed?

Cancer mortality risk coefficients in the LSS were developed by using two Poisson regression models: (1) purely additive and (2) purely multiplicative. Transfer of risk coefficients from the LSS cohort to other populations can be done with three models: (1) additive, (2) multiplicative, and (3) NIH. Although the additive transfer method results in transferred risk coefficients (for the U.S. population) that are half those obtained with the multiplicative or NIH methods, EPA based its transfer uncertainty only on the multiplicative and NIH methods. EPA should use all three transfer models for assessing transfer uncertainties.

Another factor that EPA might consider in generalizing radiogenic cancer risk from the survivors of the atomic bombings of Hiroshima and Nagasaki to the U.S. population are genetic diversity and individual variation in radiation response. Studies in population genetics now indicate that the human genome contains “cancer-predisposing genes,” which specifically play an important role in controlling programmed cell death (apoptosis), cellular proliferation, and DNA repair pathways (Sankaranarayanan and Chakraborty, 1995) (See Appendix B).

b) Is the overall approach to quantifying and combining uncertainties appropriate?

In an effort to obtain a single parameter to represent both the NIH (1985) and multiplicative transfer functions (ICRP, 1991), EPA estimated the geometric mean coefficient (GMC) for risks from both models. In this fashion, EPA did not assign subjective weights to each transfer model, but rather combined the two sources of uncertainty into a hybrid of the two, and then treated the combined uncertainty as a single probability distribution for sampling. It would be an improvement if EPA instead assigned a subjective probability weight to each transfer model (additive, multiplicative, NIH), rather than using a geometric mean coefficient for the results of just the latter two approaches. The subjective weighting method assigns a "score" to each model, which is determined as the ratio of each model's total risk to the sum of risks for all models. The probability density of each model is then sampled and weighted according to the model's score, and combined over many iterations (e.g., 5000) into a final mixture model. As additional information becomes available, the currently specified subjective probability distributions should be updated objectively, using a an intellectually consistent approach (such as a Bayesian process) to reflect improvements in the state of knowledge. Opportunities for updating should be encouraged, and incentives provided, when uncertainty levels are too high to permit confident decision making.

c) *Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?*

New information on transfer of risk based on cancer incidence indicates much wider variation across sites, gender, and age when compared with transfer of mortality risks under similar projections (NCRP, 1997).

The NCRP (1997) report concluded that comparisons between multiplicative and additive transfer for cancer incidence risks varied by factors of two to three, while for mortality risks the ratio of multiplicative to additive transfer was on average unity. Therefore, the mortality-based approach used by EPA does not account for the wider variation (greater uncertainty) observed when transferring incidence data.

3.4 Errors in Dosimetry

Errors in dosimetry include random errors in the original doses assigned to the individuals within the LSS cohort, uncertainty in the estimation of neutron doses, bias in gamma ray estimates, uncertainty in the characterization of radiation shielding by buildings, and uncertainty in the neutron relative biological effectiveness (RBE). EPA's estimates of the combination of these five sources of uncertainty are taken directly from

NCRP Report No. 126 (NCRP, 1997). For the risk of cancer mortality due to low-level, low-LET, whole body irradiation the distribution of uncertainty as a result of possible errors in dosimetry is characterized by a unitless bias correction factor represented by a normal distribution with a mean of 0.84, and a standard deviation of 0.11. For the risk of fatal lung cancer from low-dose irradiation of the lungs, a normal distribution is assumed by EPA with a mean of 0.75 and a standard deviation of 0.15. The latter assumption is also used for leukemia from low-dose irradiation of the bone marrow. Whether the error distributions are appropriate is of concern to the Subcommittee and we commend EPA for itself questioning that point. The Subcommittee's findings on the relevant aspects of the Charge follow:

a) *Are the relevant sources of uncertainty addressed?*

The relevant sources of dosimetry error are addressed with respect to the dosimetry of the LSS. The state of knowledge on this dosimetry, however, has continued to evolve. Thus, it is recommended that the newest literature, especially that related to the dosimetric contribution of fission neutrons, be reviewed. This includes Straume,*et al.* (1992), and Straume (1996; 1998).

b) *Is the overall approach to quantifying and combining uncertainties appropriate?*

Random errors in the Radiation Effects Research Foundation dosimetry (RERF, 1992) are discussed in Section E of the October 1997 draft EPA report (EPA, 1997). The text states that such errors result in an overestimate of doses for the high-dose groups, but neglects to state that the doses for the low-dose groups may be underestimated. It should be noted that random errors will affect the entire dose range. In some cases, e.g., for the A-bomb survivor data, the magnitude of the uncertainty is dose dependent, resulting in different degrees of distortion over the range of estimated doses. Random errors will in general increase the range of estimated doses to be greater than the true range, and result in a bias of the slope towards lower risk (Pierce and Vaeth, 1991).

The EPA text states that the dose response relationship (risk estimates) will be biased downward by roughly 10%. This estimate is probably sufficient, though possibly on the low side. Present views of RERF staff are that although the random errors for the LSS doses might approach 45%, the downward bias in the risk estimates probably does not exceed 10 to 15% (Donald Pierce, private communication).

c) Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?

The description of types of possible errors in the RERF dosimetry seems comprehensive given the state of knowledge today. However, EPA fails to explain that random errors affect the entire dose range, rather than just the high dose groups. EPA notes that a true quadratic shape may be distorted downwards. Similarly, Table 3.3 in NCRP Report 126 (NCRP, 1997; shows that correcting for distortion in a quadratic relationship can increase the quadratic (high-dose) coefficient several fold, resulting in a much steeper curve at high doses. The implications of this concept should be explored in more detail so as to determine whether a large downward bias of the slope of the quadratic dose-response curve (before adjustment for random errors) could be operative at dose levels of concern. In that case, risks could currently be underestimated significantly.

EPA questions whether the total dosimetry error distribution derived by Report No. NCRP 126 is adequate, and EPA should be commended for this. NCRP and EPA assumed that the sub-components of the dosimetry-related error terms were uncorrelated; thus, it is possible that the magnitude of the total dosimetric uncertainty is underestimated. Recognizing the possibility that the dosimetric uncertainty is underestimated, EPA notes: "...we have adopted the distribution recommended by the NCRP for each site where the risk model is derived from the LSS data." EPA should explicitly describe the distribution for each site and explain how adopting those models eliminates the likelihood of underestimating dosimetric uncertainty. Table 4 should also be modified accordingly, as it suggests a single distribution to characterize dosimetric uncertainty.

3.5 Low Dose Rate Extrapolation of Low-LET Risk Estimates

The extrapolation of observed excess cancer deaths among the atomic bomb survivors receiving acute doses of 0.1 to 4 Gy to that expected for a similar population exposed to low doses delivered at low dose rates is usually the most important source of uncertainty in estimates of risk from environmental exposures to low-LET radiation. For the risk of cancer mortality due to low level, low-LET, whole body radiation, EPA assumes a unitless multiplicative bias correction factor used to reduce the effect observed for acute doses. This factor is referred to as the low dose and dose rate effectiveness factor (DDREF). The DDREF is applied in the denominator of EPA's equation for estimating radiogenic cancer risk. The uncertainty in the DDREF is represented as a trapezoidal distribution with a range of 1.0 to 5 and the most likely

values occurring between 1.0 and 2.0. The same distribution is used for the risk of fatal lung cancer from irradiation of the lungs. For leukemia from irradiation of the bone marrow, a lognormal distribution is assumed with a geometric mean of 2.5 and a geometric standard deviation of 1.5. Specific issues of the Charge are:

a) *Are the relevant sources of uncertainty addressed?*

The URRS concurs with the EPA's decision (for the purpose of uncertainty analysis) not to address the potential for the occurrence of a threshold or beneficial effect at very low doses, since the probability of such effects cannot be quantified, given the data currently available (EPA, 1977; NCRP, 1997).

b) *Is the overall approach to quantifying and combining uncertainties appropriate?*

For most biological effects, the effectiveness of low-LET radiation varies as a function of the dose rate, whereas the effectiveness of high-LET radiation is relatively dose-rate independent (NCRP, 1990). Thus, a given dose of low-LET radiation is generally thought to be more effective if absorbed in a matter of seconds or minutes than if absorbed gradually over a period of hours or days. In laboratory animals the carcinogenic effectiveness of a given dose of low-LET radiation may vary by a factor of two or more, depending on the dose, the dose rate, the type of cancer in question, the age of the population at risk, and other variables (NCRP, 1980, 1990; UNSCEAR, 1986; 1988; Sinclair, 1993).

Although the influence of the dose rate has been well documented in experimental model systems using laboratory animals and biological cultures, there is as yet little quantitative information about its influence on the carcinogenicity of low-LET radiation for humans. For humans, the relevant epidemiological data are limited thus far largely to observations at relatively high doses and high dose rates (Vaeth*et al.*, 1992). Extrapolation from the existing data to estimate the human cancer risks attributable to low-level irradiation is, therefore, fraught with considerable uncertainty.

The various uncertainties that are involved in extrapolating to low doses and low dose rates have been discussed at length in each of several recent authoritative reviews of radiation risk assessment (NAS/NRC, 1990; ICRP, 1991; UNSCEAR, 1993; NCRP, 1993, 1997).

From review of the available data, the following conclusions appear to be warranted:

(1) The value of the DDREF may be influenced by a number of variables, the effects of which cannot be estimated with confidence from the data that are now available.

(2) The values for the DDREF that have been recommended by NCRP and other expert bodies represent uncertain estimates of the average DDREF value and should not be assumed to apply in all circumstances, to all cancers, or to all individuals.

(3) Although available data argue strongly against a nominal DDREF value that is substantially less than 1.0 (UNSCEAR, 1993), for some cancer sites (e.g., breast cancer), the evidence suggests that the value could be as low as 1.0, and some probability should be given to the possibility of values being somewhat less than 1.0.

4) At the upper end of the range of potential DDREF values, on the other hand, values in excess of 5.0 are not ruled out, since, as stated in the BEIR V report (NAS/NRC, 1990), "At low doses, a model dependent interpolation is involved between the spontaneous incidence and the incidence at the lowest doses for which data are available." "Moreover, epidemiological data cannot rigorously exclude the existence of a threshold in the millisievert dose range."

5) For some sites (e.g., lung cancer), the values of the DDREF could be large.

c*)* *Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?*

The subjective distribution should include the possibility of values of DDREF being less than 1.0 for certain cancer sites and greater than 5.0 for very low doses and dose rates. If values less than 1.0 are not plausible, then a subjective weight should be given to the probability that a DDREF of unity is indeed the true value.

3.6 Uncertainties in the RBE for Alpha Particle Radiation

EPA has also addressed the uncertainty in the RBE factor for high-LET radiation from alpha particle emitting radionuclides. This pertains to the uncertainties in the application of risk estimates to the intake of alpha-emitting radionuclides, rather than to the uncertainty in the risk estimates themselves, which was addressed in other sections of the EPA draft document. For the induction of cancer mortality from solid tumors, a lognormal distribution of possible values for the RBE is assumed with a geometric mean of 14.1 and a geometric standard deviation of 1.9, corresponding to a 90% subjective confidence interval of 5 to 40. These values have no units since the RBE is a unitless quantity. For leukemia induced from alpha-emitting radionuclides deposited in the mineral bone, the uncertainty of the RBE is described as a uniform distribution ranging from 0 to 1.0. Leukemia induced by alpha-emitting radionuclides not deposited in or on the bone is assigned a lognormal distribution with a geometric mean of 3.0 and a geometric standard deviation of 1.7, corresponding to a 95% subjective confidence interval of 1 to 10. For the lungs, the same distribution of the RBE is assumed as for other solid tumors. Uncertainties in the RBE for liver and bone are considered by EPA to be negligible since low-LET radiation of these sites should not result in a major contribution of the total risk induced from the intake of beta or photon emitters. Findings addressing the Charge follow below:

a) *Are the relevant sources of uncertainty addressed?*

The uncertainties associated with the concept of RBE, itself, are not addressed (See Appendix C).

b) *Is the overall approach to quantifying and combining uncertainties appropriate?*

Given the many uncertainties in each of the phenomena contributing to RBE, it is highly appropriate to try to bound the problem. Such an attempt is synonymous with accounting for lack of knowledge. The EPA attempt to estimate the bounds of knowledge has been credibly undertaken; there is no right or wrong answer at this time.

Section G of the EPA draft is a fair statement of the uncertainties associated with RBE values. That RBE values may vary with the biological endpoint of interest was recognized and addressed by assigning RBE values to two endpoints for which there are epidemiological data, leukemia and lung cancer. This is about as much as can be done at the present time due to limited epidemiological data. It might be possible to use the thorotrast (a 25% solution of thorium dioxide) and radium epidemiological databases from BEIR IV (NAS/NRC, 1988) to

derive an RBE for alpha irradiation of liver and bone, respectively. However, in spite of the presence of low levels of alpha-emitting radio nuclides in the work-place, the environment, and in medical uses, relatively few cases of human cancer caused by alpha emitters at low doses have been recorded, thus severely limiting the epidemiological database.

c) *Are the mathematical functions used to characterize the various sources of uncertainty reasonable in view of available scientific information?*

Adjustments might be warranted to account for the uncertainty of the RBE concept, itself, which may dwarf other RBE uncertainties addressed in the EPA draft. Quantifying this would be very difficult and subject to considerable debate. This might be an area warranting a formal expert elicitation.

EPA might consider an additional evaluation of model uncertainty for risks of high-LET radiation. The draft EPA uncertainty document calls attention to the uncertainty of RBE, particularly with regard to alpha radiation. Even so, the uncertainties may be understated. An alternative to RBE is suggested, but it is applied only to radium-induced leukemia and radon-induced lung cancer. This leaves a very uncertain RBE value of 20 to be applied to alpha radiation in all other situations. The RBE concept is not unassailable, because it produces risk estimates that do not always conform with observed cancer risks in humans exposed to radon or radium. The usual argument is that the dose from these alpha emitters is not uniform in the target organ and that proper microdosimetry would confirm the RBE estimates. However, other models such as ones that depend on chemical as well as physical properties of the alpha emitters might be contemplated. Moreover, the DDREF concept is conventionally stated to be different for alpha radiation than for beta or gamma radiation, putting further strain on the concept of a universal risk coefficient for RBE-adjusted dose. The draft document acknowledges the difficulties of RBE by using non-LSS studies to define risks for radon and radium, but the reliability of risk estimates for other alpha emitters is not well understood.

3.7 Accounting for Additional “Unknown” Sources of Uncertainty

The task undertaken in the October, 1997 EPA draft document describing uncertainty in radiogenic cancer risks is similar in scope to the NCRP Report number 126 (NCRP, 1997). The NCRP document includes a multiplicative correction factor to "...account for unknown uncertainties, some identified but not allowed for and others assumed to exist but not identified." This Subcommittee examined the method and

rationale for the additional factor used by NCRP and whether EPA should include a similar factor. The following guidance is offered: If significant sources of uncertainty can be identified, but not quantified, some adjustment might be necessary. This adjustment could take the form of a multiplicative distribution with a mean of unity and a variation to be subjectively determined. However, if sources of uncertainty are only suspected, but cannot be identified (and of course not quantified), no adjustment should be attempted.

The Subcommittee bases its guidance on the concept that a reasonable degree of belief regarding a factor must be present to form subjective confidence intervals. This concept was described by Morgan and Henrion (1990): "Even from the personalist or subjectivist view, an event or quantity must be well-specified for a meaningful probability distribution to be assessable." Thus, the difficulty in defining a "catch-all" parameter to account for uncertainties from unknown sources, is that it cannot be specified. If it could, then the sources of uncertainty to be accounted for by the "catch-all" parameter should be treated explicitly.

The decision of EPA not to include such a parameter in its calculations is sensible. We support such an approach because it constrains subjective judgment to those situations where evidence, or at the very least, prior experience, is the basis for parameter estimation.

4 CONCLUSIONS AND RECOMMENDATIONS

The Subcommittee commends EPA for producing a generally credible approach to characterizing the uncertainty in radiogenic cancer risk estimates. References to the corresponding sections of the detailed discussion in Section 3 appear in parentheses.

4.1 Risk Estimates Based on Cancer Incidence Rather than Cancer Mortality

Given the additional uncertainty introduced from use of mortality data, in future efforts to improve on its quantification of radiogenic cancer risk and its associated uncertainty, EPA should consider developing risk estimates for the U.S. population based primarily on transfer of cancer-incidence based risks from Japanese atomic bomb survivor studies (Mabuchi *et al*., 1998; Thompson *et al*., 1994; Preston *et al.*, 1994); EPA should not rely entirely on mortality risks for this transfer (Shimizu *et al*., 1990). This shift would allow EPA to eliminate transfer uncertainty related to lethality fractions (cancer survival rates), which vary among countries and over time within any single country. Incidence-based risks would also allow EPA to (1) account for the larger variation in transfer when compared with transfer of mortality risks (NCRP, 1997), and (2) transfer absolute and multiplicative risks on a site-, gender-, and age-specific basis, which is more biologically meaningful. (Section 3.1.2)

4.2 Alternative Modeling Approaches for Transferring Risk Estimates

EPA should consider the additive, multiplicative, and NIH models as alternative modeling approaches for transferring radiogenic cancer risk coefficients from the LSS cohort to the U.S. population. EPA should consider assigning a subjective weight to each model (additive, multiplicative, and NIH), rather than using a coefficient based on the geometric mean of the latter two approaches. Furthermore, as additional data become available, the subjective weight initially assigned to the different models should be updated to get posterior probabilities for the validity of the different models.

4.3 Clarification of Uncertainty Distributions

EPA derives the uncertainty of cancer risk estimates by assigning distributions to uncertainty bias correction factors and combining these distributions by numerical techniques. However, it is not made clear that each distribution is defined to represent the state of knowledge about the value of that parameter that would be relevant to an average member of the population. The Subcommittee recommends that EPA clarify the risk assessment objective and carefully define each uncertainty distribution in terms of that objective and in terms of the current state of knowledge. This clarification would eliminate any likelihood of readers mistakenly assuming that the distributions represent empirical variation. (Section 3.2 (b))

4.4 Uncertainty in the DDREF

The uncertainty in the DDREF should reflect the current state of knowledge. The subjective probability distribution for extrapolation from high to low dose rates for low-LET radiation should include a greater weight to the possibility that the DDREF could be less than or equal to 1.0. A non-zero weight should also be considered for DDREF larger than 5.0. In any case, stronger justification is needed to explain why a subjective weight is not given for values exceeding 5.0. The values chosen for DDREF could also vary depending on the type of cancer and organ affected.

4.5 Future Updates of the Uncertainty Analysis

Multiplication of probabilities to obtain the joint probability is appropriate only for statistically independent quantities. Possible dependence of the quantities multiplied together should be investigated. This issue is especially pertinent for the dependency of statistical sampling errors on diagnostic misclassification of cancer mortality.

Parts of the EPA approach to uncertainty analysis should be changed in the future. It is recommended that subjective probability densities be used initially to describe uncertainty and that these probability densities be updated with available data. Subjective assessment of the uncertainty of quantities is usually the starting point of a Bayesian analysis. The next step involves use of available data to update and to reduce the uncertainty with the likelihood of the probability model under consideration. At the present time, EPA's subjective assessments do not provide for updating. EPA's uncertainty assessments should be a living process that allows updating the present subjective probability distributions as more data become available, and could make the entire process more objective and amenable to refinement with advances in the state-of-the-art. This will eventually lead to a consensus.

4.6 Subjective Distributions Based on Expert Elicitation

For those inputs that dominate the overall uncertainty in radiogenic cancer risk, use of more formal methods of expert elicitation would be desirable to obtain defensible estimates of subjective distributions that reflect the current state of knowledge. Formal elicitation of expert judgment would be preferred to informal estimates made by EPA staff. Currently, the subjective probability distributions specified by EPA staff reflect only the state of knowledge of the EPA. A more formal elicitation would encompass an evaluation of extant data sets by a broader spectrum of expertise both inside and outside of EPA. This is the approach recommended in NCRP Commentary No. 14 (NCRP, 1996). (Section 3.6)

4.7 Treatment of Unknown Sources of Uncertainty

The Subcommittee believes that the EPA has used uncertainty analysis methods in a credible and defensible way to quantify uncertainty and should not attempt to assign distributions to so-called “unknown” sources of uncertainty which can neither be identified nor quantified. Such methods were used in NCRP Report No.126 (NCRP, 1997), but some of the assumptions used in the NCRP document go beyond the weight of the evidence. The Subcommittee believes that the EPA should examine whether their calculated range of risk is sufficient to include what are believed to be possible values of the true dose response, and should provide adequate adjustments or commentary if such is not the case. (Section 3.7)

APPENDIX A - THE COMPARISON OF MORTALITY VERSUS INCIDENCE DATA

The purpose of the EPA October 1997 Draft Addendum was to describe a methodology for estimating uncertainties in the EPA risk projections for cancer mortality estimates. While we understand that this was the Charge given to EPA and the National Council on Radiation Protection and Measurements, we have significant reservations about the usefulness of a document that focuses solely on mortality rather than on incidence data. Given the availability of incidence data since 1958 and the many problems inherent in using mortality statistics upon which radiation protection standards could appropriately be based, it would seem reasonable to revise the approach taken in radiation protection to one of protecting individuals from exposures that place them at increased risk of developing cancer, rather than protecting them from exposures leading to an increased risk of dying from cancer. Further, the use of mortality as the sole endpoint of concern is inconsistent with most of EPA's risk assessments, which are based on disease incidence. Incidence data from the LSS are available and should serve as the primary basis for EPA's estimates of radiogenic cancer risk .

Although mortality data derived from death certificates have served as the basis for many epidemiologic studies over the years, the accuracy and utility of death certificate data on underlying causes of death have been called into question when compared to hospital records, autopsy information, or data from tumor registries (especially the last). Studies in the U.S. and Japan have evaluated the use of death certificate data as the basis for calculating risk estimates and found these data to be inaccurate and of limited use because a) mortality risks as an index of harm underestimate incidence rates; b) death certificate-based mortality risks do not reveal patterns of risk and survival by stage of cancer and histological cell type; c) death certificate-based mortality cannot include risk for benign (non-fatal) cancers; and d) death certificate-based mortality risks require an additional bias correction for diagnostic misclassification (Chao and Devesa, 1996; Gittelsohn and Senning, 1997; Hoel *et al*., 1993; Kircher *et al*., 1985; Percy *et al*., 1981; Percy *et al.*, 1990). Therefore, data on the incidence of disease are preferred over mortality statistics when estimating exposure-response risk coefficients.

It is not surprising that diagnostic misclassification tends to be much less of a problem with tumor registry than death certificate information. Tumor registries typically draw information from a variety of sources such as clinical and pathology records, as well as from death certificates. Diagnoses are usually verified histological ly and are reportable to the tumor registry within a year of diagnosis. Individuals who complete registry information forms are specifically trained to abstract accurately information from all appropriate sources. An incidence-based approach is affected less by cancer misclassification than when compared with a mortality-based approach. The

authors of the October 1997 Draft Addendum themselves acknowledge that "...studies at the level of incidence are inherently more accurate than mortality-based studies using death certificate diagnosis for classification... " (EPA, 1997; page 18).

Migration of exposed individuals is not a reason to abandon incidence data in favor of mortality data. It is important to note that in the LSS study, the occurrence of cancer and the record of this occurrence (i.e., the tumor registry) are really part of a cohort study rather than part of a geographically constrained plan used in many registry designs. Further, it is also important to note that death certificates are routinely included by registries as an important source of information on cases not ascertained through other means.

Studies in the US have shown that, overall, hospital discharge abstracts, cancer incidence registries, and autopsy results agree with death certificates only 65% to 77% of the time (Kircher *et al*., 1985; Gittelsohn and Senning, 1979; Percy *et al*., 1981, 1990). Accuracy of death certificate data decreases significantly when the certificates are evaluated for appropriate subtype of cancer within a particular organ system and with increasing age of the decedent (Chow and Devesa, 1996).

Because of the very large autopsy series among A-bomb survivors, there is a considerable amount of data on the accuracy of death certificate information during the period 1961 to 1987 as part of the LSS (Hoel *et al*., 1993). The autopsy program showed that the death certificate detection rate for total cancer was 79%, while the autopsy confirmation rate was 93%, corresponding to an underestimate of the number of cancer deaths by 18%. These numbers varied depending on the specific cancer site. For example, the underestimate for lung cancer was 33%. Among cancers of interest in radiation carcinogenesis, the detection rate (rate at which true cases of cancer are detected) for respiratory sites was 54%, for breast 76%, and for hematopoietic cancers 68%. When death certificates were compared with tumor registry information, there was considerable underestimation for some cancer sites. For liver cancer, for example, confirmation (rate at which cases of cancer are classified accurately) was 34%, while detection was 55%. Further, the quality of death certificate information has been a problem when deaths are studied over time and over age groups. Detection and confirmation for a number of sites have improved over the years, particularly for the older age groups, 75 years and above. The result is a shifting baseline upon which static conclusions are based. Thus, the very use of mortality rather than incidence data is an important source of uncertainty.

Migration has been cited as a reason to use mortality rather than incidence data as the source of information. In the LSS Study, tumor registry data provide an invaluable source of information. Errors introduced as a result of migration of individuals from the study area, however, should be readily correctable by including information from death certificates obtained from across the country and by either

treating the death as a cancer case incidence as of the year of death or retrospectively creating a tumor registry record following an investigation of available clinical and pathology information.

APPENDIX B - GENETIC DIVERSITY AND INTERINDIVIDUAL VARIATION IN RADIATION RESPONSE

Justification for transferring radiogenic cancer risks coefficients in Hiroshima and Nagasaki atomic bomb survivors to other populations is based on strong dose-response gradients, repeated consistency with results from animal studies (and other human studies), and findings from molecular biology that have confirmed that radiation is a known carcinogen. When projecting future risks among other (non-Japanese) populations, one assumes that risk applies equally to each individual because variation in response at the individual level is unknown and is currently not well understood. As more becomes known about the genetic and environmental influences on radiation dose-response, there will be an increasing tendency to control for such factors when projecting risks. At present, however, the theoretical framework for assigning individuals to various subpopulations based on cancer predisposition is only beginning to be understood.

Studies in population genetics now indicate that the human genome contains "cancer-predisposing genes," which specifically play an important role in controlling programmed cell death (apoptosis), cellular proliferation, and DNA repair pathways (Sankaranarayanan and Chakraborty, 1995). For example, two autosomal recessive disorders known as xeroderma pigmentosum (incidence of 1/100,000 to 1/250,000) and ataxia telangiectasia (incidence of 1/90,000 to 1/300,000) confer high radio sensitivity for UV-related skin cancer and increased reaction to radiation therapy, respectively, as a result of defects in DNA repair/replication (Kraemer *et al*., 1984; Bender *et al*., 1985; Kraemer *et al*., 1987; Gatti *et al*., 1991; Swift *et al*., 1991).

The body of information on increased radio sensitivity for radiation-induced cancer among carriers of both recessive and dominant mutations is limited. However, given what is already known about cancer predisposing genes, there is sufficient evidence to assume that certain mutation carriers are at increased risk of radiation-induced cancer. To this end, Chakraborty and Sankaranarayanan (1995) recently introduced a population-based model for Mendelian inheritance of a single-gene mutation that combines cancer predisposition and radio sensitivity. Their modeling indicates that, when considering single-gene mutations for which there is likely increased cancer predisposition and radio sensitivity, an increase in radiation-induced cancer in the general population is only likely when the proportion of cancers due to predisposition is large and when the radiation sensitivity differential is considerable. For small effects of heterogeneity, a large portion of radiation-induced cancers would likely occur among predisposed individuals. When less than 10% of excess cancers are due to a susceptibility genotype, as may be the case for the presence of mutations in the breast cancer genes *BRCA1* and *BRCA2* among non-Ashkenazi women with breast cancer, a marked increase in relative and attributable risk is only seen when

there is a greater than a 1000-fold increase in cancer susceptibility and a greater than 100-fold increase in radio sensitivity. (Chakraborty*et al*., 1997).

Relatives of individuals with susceptibility genotypes are also presumed to be at increased risk of radiation-induced cancer in comparison with un-related individuals. Chakraborty, Little, and Sankaranarayanan (1998) modeled proband genotype frequencies using Hardy-Weinberg expectations and determined that risk of radiation-induced cancer increases with the degree of relatedness, with higher risk occurring for close relatives and lower risks occurring for distant relatives. For recessive genotypes, this relationship drops off very quickly, while for dominant genotypes less quickly. In addition, they suggested that epidemiologically-based detection of increased radiation-induced cancer in related individuals is only possible for commonly occurring mutant alleles and conjointly dramatic predisposition and radio sensitivity. A major observation that arose from the modeling work of Chakraborty, Sankaranarayanan, and Little was that in a multi-gene scenario, where more than one susceptibility gene is sufficient for causing disease, the effects of irradiation could possibly be higher than in a single-gene framework.

APPENDIX C - UNCERTAINTIES IN THE RBE FOR ALPHA RADIATION

The discussion in the draft about uncertainties in the RBE (relative biological effectiveness) for alpha radiation and the need to draw upon epidemiology data to assign values of RBE for lung cancer and leukemia raises old questions about the validity of the RBE concept and whether it is possible to achieve the conditions required to determine RBE values as defined. The RBE for a radiation of interest is defined as being equal to the dose of reference radiation (x- or gamma radiation) required to produce a specific level of response divided by the dose of radiation of interest to produce an equal response. To make a determination of RBE, all physical and biological variables are to be held constant with the exception of radiation quality (NCRP, 1990). This conceptual requirement introduces a major uncertainty into any determination of RBE.

First, there are few circumstances where it can be assured that the distribution of energy from the radiation of interest to the cells or tissues in which the biological response occurs is exactly the same as the distribution of energy from the reference radiation to the same cells or tissues. While the reference radiation generally can be expected to irradiate all cells and tissues equally, alpha radiation and most beta radiation will irradiate cells and tissues non-uniformly. This nonuniform distribution may be enhanced if the radiation originates from nonuniform deposits of radio nuclides in the body and tissues, even more so if it originates from particulate sources rather than from molecules of radioactive material distributed uniformly throughout the body. Lack of knowledge about both the spatial distribution of absorbed energy within the organ and tissue and the spatial distribution of target cells leads to a serious dosimetry problem (At one time, prior to ICRP Publications 26 and 30 (1977, 1979), a factor, N, was incorporated into dose calculations in addition to the quality factor, Q, to account for nonuniform distribution of deposited radio nuclides, especially in bone). Although there were considerable uncertainties associated with this practice, they were probably not lessened when N was dropped. Relating risk directly to exposure, eliminating the calculation of dose, is another approach that has been considered occasionally as a way of getting around the uncertainties of RBE as well as those of dosimetry and dose-response models.)

Second, it is rare that the rate of energy deposition in the cells and tissues in which the response occurs is the same for the reference radiation and the radiation of interest. Most alpha emitters are long-lived; this raises questions about the turnover rates of sensitive cells relative to the radionuclide's physical half-life and suggests that the same cells may not remain as targets while the radionuclide continues to decay and that many generations of cells may be irradiated by a given deposition of a radionuclide. The radionuclides themselves may migrate within the body and within tissues, further confounding the dosimetry problem. Radon presents a different picture. Since the half-lives of radon decay products are so very short, delivering energy to

affected cells at high rates, the RBE for radon might very well differ from those of other alpha emitters.

Third, the biological response caused by the radiation of interest is not always the same as that caused by the reference radiation. For example, while alpha and gamma radiations may both elicit tumors, the tumor types may be different for a variety of reasons, including the fact that different cells may have been irradiated. Estimates of cancer risk determined from the LSS and other populations exposed to low-LET radiations are generally applied to estimate the risks from intakes of internal emitters. It is assumed that uniform irradiation of a tissue yields the same effects and risks as nonuniform irradiation by internal emitters. In the case of alpha emitters, in particular, this assumption results in estimates of the occurrence of health effects from internal emitters that have never been observed in either experimental animals or exposed human populations. A case in point is chronic myelogenous leukemia (CML), which can be caused by exposures to external x- and gamma radiations. It has been assumed that CML may also result from intakes of radionuclides that deposit in bone. However, not all radionuclides that deposit in bone, particularly on bone surfaces, emit radiations that penetrate to the appropriate sensitive cells. An example is plutonium, an alpha-emitting bone seeker. No case of CML has been observed in thousands of experimental animals or humans exposed to plutonium (it has been observed only in a few rodents given highly soluble forms of plutonium, resulting in a high incidence of bone cancers, including cases in those animals that also developed CML). Of the cancer sites given in Tables 1 and 2 of the Draft Document (EPA, 1997), only the lung sites are relevant to plutonium (for soluble forms of plutonium, liver and bone should be added), yet risks calculated for other tissues which have not really been shown to be at risk are included in the summation of the total risk, using the Effective Dose formulation. Total risks calculated in this manner, particularly when doses to non-responsive tissues are significant, may be less than those calculated by the EPA approach, which calls for summing the risks calculated separately for each tissue (EPA, 1997). This situation is more likely for radionuclides that do not deposit uniformly in the body.

The application of an RBE value to a radiation exposure situation in which dose is either modeled or measured in a way different from that in which the RBE value was determined contributes further uncertainty to the applicability of RBE. This additional uncertainty may be relevant to EPA's decision to use a distribution of RBE values for alpha radiation that is uniform from 0 to 1.0 for leukemia. As noted in the Draft Document, another explanation for the relative ineffectiveness of alpha radiation in producing leukemia could be that alpha particles do not reach the sensitive cells, and because of this limited range, the doses to critical cells are overestimated (EPA, 1997). The same limitation in range can apply to other tissues including the respiratory tract. The radiation-insensitive thoracic lymph nodes are at one end of the spectrum; they receive the highest dose when insoluble plutonium is inhaled. Application of an RBE of

20 to these doses, which apparently do not reach sensitive cells, would give extremely high risk estimates, when in fact the risk has been shown to be essentially zero at all doses. At the other end is the more radiation-sensitive bronchial epithelium, which receives much lower doses, but application of an RBE of 20 could still lead to overestimates of the risk of cancer originating in this tissue.

The difficult, if not impossible, task of deriving RBE values for internal emitters is well known. In ICRP Publication 31, *Biological Effects of Inhaled Radionuclides*, it was recognized that derivation of RBE values for alpha emitters that would meet the strict definition of RBE (see above) was not possible for the primary reason that nonuniform dose distribution occurs in nearly all cases of alpha emitters in the body (ICRP, 1980). The quantity RBE is likely a parameter which lumps together several distinct phenomena. In its place, an Equal Effectiveness Ratio was proposed that included differences in dose distribution in affected tissues (average tissue doses were calculated, assuming uniform distribution of energy, for both alpha emitters and beta/gamma emitters) as well as differences in RBE. This approach gave Equal Effectiveness Ratios from 6 to 40 (often erroneously quoted as RBE values), depending upon the dose ranges compared. If the differences in dose distribution within affected tissues could be removed, then RBE values lower than the nominal value of 20 for alpha emitters would likely be obtained. The Draft EPA Uncertainty document (EPA, 1997) in effect acknowledges this expectation of lower RBE values for radium-induced leukemia and radon-induced lung cancer, preferring to use epidemiology data that suggest RBE values of one for radium-induced leukemia and 10 for radon-induced lung cancer. This adoption of RBE values less than 20 in itself recognizes the lack of coherence in the dose-risk approach using the LSS data.

The fact that the basis for our system of radiation protection is not internally consistent, with risks calculated by applying risk factors to doses rarely in agreement with risks obtained from epidemiology, is indicative of the uncertainty problem. One area of uncertainty is clearly the interpretation of the LSS data, but greater uncertainties may occur in applying the results of the LSS data to other types of radiation exposures. This issue of transferability has been considered by numerous committees and individuals with respect to chronic low-LET external radiation but less so for internal emitters, especially high-LET alpha radiation. Attempts to apply risk estimates for lung cancer derived from LSS data to radon exposures, using the accepted values for DDREF and RBE along with current lung dosimetry, have been discouraged by the ICRP because they lead to estimates that exceed those obtained from epidemiological studies of miners (ICRP, 1993). This lack of agreement with epidemiology suggests uncertainties in the process, which could be associated with the risk factor itself, with the values of DDREF and RBE used in the calculations, and, of course, with the dose models. This aspect should receive greater attention in the EPA draft document on Uncertainty Analysis (EPA, 1997).

Since RBE values for a radiation of interest may vary greatly depending upon the biological response being measured, the test subject, the magnitude of the dose, etc., single RBE values are of questionable utility. The current use of a radiation quality factor, Q, and more recently W_R, the radiation weighting factor (a replacement for Q), based more on linear energy transfer of the radiation than on biology, probably introduces even more uncertainty, but the practice has merit in not requiring use of multiple RBEs in calculations of effective dose.

APPENDIX D - ACRONYMS

ABCC	Atomic Bomb Casualty Commission
BEIR	Biological Effects of Ionizing Radiation
Bq	Becquerel (1 disintegration per second)
BRCABRCA1 & BRCA2	Breast Cancer Genes
CCI	Classical Confidence Interval
CML	Chronic Myelogenous Leukemia
Ci	curie ($3.7x10^{10}$ disintegrations per second)
DDREF	Dose and Dose Rate Effectiveness Factor
DNA	Deoxyribo Nucleic Acid
EPA	U.S. Environmental Protection Agency (U.S. EPA)
GMC	Geometric Mean Coefficient
Gy	Gray (One joule per kilogram of absorbed energy)
ICRP	International Commission on Radiological Protection
LET	Linear Energy Transfer
LSS	Lifespan Survivor Study
N	A factor incorporated into dose calculations, in addition to the quality factor, Q, to account for nonuniform distribution of deposited radionuclides, especially in bone
NAS	National Academy of Sciences
NCRP	National Council on Radiation Protection and Measurements
NIH	National Institutes of Health (U.S. NIH)
NRC	Nuclear Regulatory Commission (U.S. NRC)
ORIA	Office of Radiation and Indoor Air (U.S. EPA/ORIA)
Q	Quality Factor
R	Uncertainty in Cancer Risk
RAC	Radiation Advisory Committee (U.S. EPA/SAB/RAC)
RBE	Relative Biological Effectiveness
RERF	Radiation Effects Research Foundation
R_{HN}	Uncertainty in Cancer Risk for the Hiroshima/Nagasaki Population
R_{US}	Uncertainty in Cancer Risk for the United States Population
RR	Relative Risk
SAB	Science Advisory Board (U.S. EPA/SAB)

SCI	Subjective Confidence Interval
UN	United Nations
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
URRS	Uncertainty in Radiogenic (Cancer) Risk Subcommittee (U.S. EPA/SAB/ RAC/URRS)
U.S.	United States
UV	Ultra Violet
w_R	Radiation Weighting Factor

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