UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

- - - Date To Be Added - - -
Working Draft of June 10, 2009

EPA-SAB-09-xxx

The Honorable Lisa Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: SAB Review of "EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population," Draft December 2008

Dear Administrator Jackson:

The Radiation Advisory Committee (RAC) of the Science Advisory Board has reviewed the draft document *"EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population*, December 2008." In this draft "Blue Book," the Agency's Office of Radiation and Indoor Air (ORIA) presents new EPA estimates of cancer incidence and mortality risks associated with exposure to low doses of ionizing radiation for the U.S. population, along with the scientific bases for these decisions. Most estimates are calculated with models recommended in the National Research Council's BEIR VII Report (NRC 2006), sponsored by EPA and other federal agencies.

The EPA sought the RAC's advice in regard to (1) the Blue Book's applications of and extensions beyond the BEIR VII Report, (2) the related uncertainty analysis, and (3) validity of its content in terms of scientific defensibility, appropriateness, presentation of calculations and results, accuracy, balance, and level of detail. The RAC's response to these three questions is summarized below:

1) The RAC agrees with the approaches proposed by EPA for estimating the cancer risks for alpha particles, low-energy beta particles, and low energy gamma and x rays that reflect relative biological effectiveness (RBE) value larger than one. ***For these low-energy beta particles, gamma rays, and x rays, insufficient information for selecting RBE values has been presented, and the RAC recommends that EPA staff encourage publication in a peer-reviewed journal of such information and proposed RBE values for review by the scientific community.***

The RAC recommends use of a weighted arithmetic mean for each set of excess absolute risk (EAR) and excess relative risk (ERR) values in transferring lifetime attributable risk (LAR) to the U.S. population from the Japanese life-span study (LSS) population. The most important reason, in the absence of a theoretical basis for either the arithmetic or the

geometric mean, is that with the arithmetic mean, the choice of weights explicitly captures judgments about the relative importance of the ERR-and EAR-based risk estimates. This approach has other benefits as well.

The RAC agrees with the approaches proposed by EPA to derive risk estimates for solid cancers not specified in BEIR VII (kidney, skin), and for that which differs from those used by BEIR VII (lung, liver, leukemia). ***The RAC recommends that, for bone, the EPA utilize the radium data for the dial painter cohort (as asserted in the Blue Book, but not done), especially applying recent analyses of the data.*** With regard to the liver, the RAC suggests the possible benefit of distinguishing among various types of cancer. For leukemia, the RAC notes the considerable uncertainty related to RBE.

The RAC compliments EPA on developing an improved model that considers the survival rate of breast cancer patients. It suggests applying this model to other cancers with high rates of survival. The RAC agrees with the EPA approach for not including in its overall risk estimates the specific risks for (1) nonfatal nonmelanoma skin cancer, that mostly are responsive to treatment, and (2) fetal exposure that in the LSS is lower than for exposed children.

2) The approach to uncertainty analysis in the draft Blue Book is reasonable and comprehensive for deriving overall risk estimate uncertainty from sampling variation, model parameters, and data transfer to the U.S. population***. The RAC recommends greater clarity and transparency in quantifying each source of uncertainty.***

The RAC recommends that the Blue Book present detailed explanations of Bayesian analysis strengths and weaknesses. The two distinct approaches to obtain best estimates and confidence intervals should be justified, and why Bayesian analysis is used for the latter.

The RAC recommends verifying the uncertainty analysis by determining uncertainty intervals by a perturbation approach. The value of each major contributor to uncertainty should be varied over a reasonable range to calculate the corresponding range of point estimates.

The RAC recommends that EPA clarify the reasoning behind the selection of distributions chosen for the sources of uncertainty. The discussion should justify the assigned distributions and trace each decision concerning central value, uncertainty, and distribution.

3) The Blue Book is scientifically defensible and appropriate. ***The RAC recommends that EPA enhance Blue Book contents by reporting further information from (1) studies of noncancer mortality; (2)re*****cent International Commission on Radiological Protection *(ICRP) and* United Nations Scientific Committee on the Effects of Atomic Radiation (*UNSCEAR) reviews; and (3) National Council on Radiation Protection and Measurements (NCRP)Report #159 on the risks of radiation-induced thyroid cancer.***

The calculations and results presented in the draft Blue Book are understandable. ***The RAC recommends for improved understanding that (1) the first chapter include a thorough discussion of EPA plans to use the Blue Book contents in preparing Federal Guidance Report***

(FGR) 13, and (2) throughout, more detailed discussions of the sources of uncertainty, their distribution, and of the Bayesian approach..

The draft Blue Book, with the suggested improvements, will have the accuracy, balance and level of detail appropriate to its intended purpose. ***The RAC recommends that improvements include: (1) reporting available studies of cohorts exposed to protracted low doses of ionizing radiation; (2) focusing on the major sources of error in uncertainty analysis; (3) considering distinguishable types of cancer within a given organ; and (4) presenting some values of radionuclide risk coefficients anticipated for FGR 13, the goal of the EPA effort.***

The RAC appreciates the opportunity to review this draft document and hopes that its recommendations will enable EPA to implement modifications in the current methods for estimating radiogenic cancer risks and update the "Blue Book" accordingly. We look forward to your response to the recommendations contained in this review.

Sincerely,

Dr. Deborah L. Swackhammer
Chair, Science Advisory Board

Dr. Bernd Kahn
Chair, Radiation Advisory Committee Augmented for Review of the Agency's Radiogenic Cancer Risk Assessment
Science Advisory Board

NOTICE

This report has been written as part of the activities of the Environmental Protection Agency (EPA) Science Advisory Board (SAB), a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use. Reports and advisories of the SAB are posted on the EPA website at http://www.epa.gov/sab.

U.S. Environmental Protection Agency
Science Advisory Board (SAB)
Radiation Advisory Committee (RAC)
Augmented for the Review of EPA's Radiogenic Cancer Risk Assessment

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1. EXECUTIVE SUMMARY

The Radiation Advisory Committee (RAC) of the Science Advisory Board (SAB) has completed its review of the Agency's draft titled *"EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population "* dated December 2008, also known as the "Blue Book." (U.S. EPA. ORIA. 2008). In the draft Blue Book, the EPA's Office of Radiation and Indoor Air (ORIA) outlined proposed changes in the Agency's methodology for estimating radiogenic cancers and estimating radiogenic cancer risk. The EPA sought the RAC's advice on its draft Blue Book to conduct the radiogenic cancer risk assessment for EPA's purposes.

The RAC responded as follows to the itemized requests for comments by ORIA:

1a. The RAC agrees with the risk estimates proposed by EPA for alpha particles, which have greater linear energy transfer (LET) than beta particles, gamma rays and X rays and higher relative biological effectiveness (RBE) values. In contrast, for low-energy beta particles (notably tritium) and low-energy photons, the RAC finds that the EPA review of information is sufficient to conclude that the RBE exceeds 1, but insufficient for selecting appropriate RBE values. ***The RAC identified several questions concerning the scientific basis and interpretation for applying an RBE larger than 1, and recommends that EPA staff encourage publiclation of suchs information and proposed RBE values for low-energy beta particles and photons for review of the scientific community in a peer-reviewed journal.***

1b. ***The RAC recommends use of a weighted arithmetic mean for each set of excess absolute risk (EAR) and excess relative risk (ERR) values in transferring lifetime attributable risk (LAR) to the U.S. population from the life span study (LSS) population.*** The most important reason, in the absence of a theoretical basis for either the arithmetic or the geometric mean, is that with the arithmetic mean, the choice of weights explicitly captures judgments about the relative importance of the ERR-and EAR-based risk estimates. This approach has other benefits as well. Any judgmentally-based preference for EAR or ERR can be expressed by the weighting factor. Neither the EPA approach nor the BEIR VII approach to calculating the geometric mean (although the former was supported in the RAC review of the EPA White Paper because of its calculational consistency) provides any calculational advantages relative to the arithmetic mean.

1c. The RAC agrees with the approaches proposed by EPA to derive risk estimates not specified in BEIR VII for solid cancers (kidney, skin), or that differed from those used by BEIR VII (liver, lung, leukemia). ***The RAC recommends that, for bone, the EPA utilize the radium data for the dial painter cohort (as asserted in the Blue Book, p.64, but not done), especially applying recent analyses of the data***. With regard to the liver, the RAC suggests the possible benefit of distinguishing among the various types of liver cancer. For leukemia, the RAC notes the considerable uncertainty related to EPA changing the RBE for low-LET radiation from 1 to 2.

1d. The RAC compliments EPA on developing an improved model that considers the survival rate of breast cancer patients. It suggests applying this model to derive risk estimates for other cancers for which the survival rates are now relatively higher than previously.

1e. The RAC agrees with the EPA approach for separating from its overall risk estimates the specific risks for (1) nonfatal skin cancer and (2) fetal exposure. Because of the high rate of spontaneous (nonradiogenic) nonmelanoma skin cancers and the experience that most nonmelanoma skin cancers are responsive to treatment, their inclusion with more serious cancers would greatly distort the overall cancer morbidity and morbidity risk estimates. The risk of adult cancer from fetal exposures observed in the LSS was lower than for exposed children, but the difference was not statistically significant; moreover, spontaneous abortions that may have occurred but were not recorded in the LSS may have distorted the data. EPA appropriately reports separate risk coefficients for children from fetal irradiation, based on X-ray exposure cohorts.

2a. The RAC considers the approach to uncertainty analysis in the draft Blue Book to be reasonable and comprehensive in deriving overall risk estimate uncertainty from sampling variation, the various model parameters, and transfer of data to the U.S. population. ***The RAC recommends greater clarity and transparency in identifying and quantifying each source of uncertainty.*** One effective technique is to discuss each contributing uncertainty to the LAR in the text and summarizing it in a table (in greater detail than is now in the Blue Book), with emphasis on the major sources of uncertainty and how they are quantified.

The RAC recommends that the Blue Book devote more discussion to Bayesian analysis to explain its strengths and weaknesses. An explanation is needed to justify two separate approaches to obtain best estimate values and confidence intervals, and why the Bayesian approach is used for the latter.

The RAC recommends verifying the uncertainty analysis by obtaining uncertainty intervals with a perturbation approach. The value of each major contributor to uncertainty should be varied over a reasonable range to recalculate the corresponding range of the point estimate to demonstrate whether the recommended uncertainty is valid.

2b. ***The RAC recommends that EPA expand the text to clarify the reasoning behind the selection of distributions chosen for the various sources of uncertainty.*** The discussion of subjective priors listed partially in Table 4.1 of the draft Blue Book should justify the assigned distributions so that the reader is able to trace the basis of each decision concerning central value, uncertainty, and distribution, and have confidence in these characteristics.

3a. The RAC recognizes the scientific defensibility and appropriateness of the Blue Book***. The RAC recommends that EPA enhance Blue Book contents by reporting further information from (1) studies of non-cancer mortality; (2) recent ICRP and UNSCEAR reviews; and (3) NCRP Report #159 on the risk of radiation-induced thyroid cancer due to Iodine-131.***

3b. The RAC found that most of the calculations and results presented in the draft Blue Book were readily understandable. ***The RAC recommends an initial presentation of the applications of models and values presented in the Blue Book; and a clearer and more transparent discussion of sources of uncertainty, their distribution, and of the Bayesian approach*** (see also 2a and 2b, above).

3c. The RAC considers the draft Blue Book to have the accuracy, balance and level of detail appropriate to its intended purpose, once the recommended revisions noted in this review are implemented. ***The RAC recommends enhancing the Blue Book by giving additional attention to the following specific items: (1) a number of available studies of cohorts exposed to low-dose protracted exposure; (2) the major sources or error in uncertainty analysis (3) distinguishable types of cancer within a given organ; and (4) a list of at least some values of radionuclide risk coefficients to indicate the ultimate products toward which the draft "Blue Book" as is directed.***

2. INTRODUCTION

2.1 Background

In 1994, the U.S. Environmental Protection Agecy (EPA) published the report, titled *"Estimating Radiogenic Cancer Risks,"* often referred to as the "Blue Book", derived from the blue cover on the document (http://epa.gov/radiation/docs/assessment/402-r-93-076.pdf). This EPA estimation of cancer risks due to low-Linear Energy Transfer (LET) radiation exposures is based on information, mainly about the Japanese atomic bomb survivors, that had become available since the publication of BEIR II Report (BEIR II 1980) and the Blue Book (EPA 1984) that followed it. The incidence of fatal cancer in specified organs and tissues per unit dose was estimated for a stationary U.S. population based on 1980 vital statistics. The effect of high-LET alpha particles also was considered in terms of their relative biological effectiveness (RBE). The 1994 report replaced the 1984 EPA report.

In 1999, an addendum to the 1994 report made minor adjustments to the previous values in terms of more recent vital statistics. The addendum also presented a partial analysis of the uncertainties in the values (http://epa.gov/radiation/docs/assessment/402-r-99-003.pdf) to provide a confidence interval for the cancer risk per unit radiation dose.

Also in 1999, the Agency applied the 1994 Blue Book contents, metabolic models, and usage patterns to publish Federal Guidance Report 13, *"Health Risks from Low-level Environmental Exposure to Radionuclides"*, with cancer risk estimates for over 800 radionuclides by several exposure pathways. (http://epa.gov/radiation/docs/federal/402-r-99-001.pdf). models and U.S..usage patterns. The data were later updated at (http://www.epa.gov/radiation/federal/techdocs.html#cd_supplement). Prior to their publications, the Blue Book and the two subsequent documents were reviewed by the EPA's Science Advisory Board (SAB).

In 2006, the National Research Council of the U.S. National Academies of Sciences (NAS/NRC) released *"Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2"*(BEIR 2006), which primarily addresses cancer and genetic risks from low doses of low-LET radiation (available at http://newton.nap.edu/catalog/11340.html#toc). The Agency was one of the sponsors of this report.

Also in 2006, EPA prepared the draft "*White Paper: Modifying EPA Radiation Risk Models Based on BEIR VII"* (EPA 2006), (available at http://epa.gov/radiation/docs/assessment/white-paper8106.pdf), in anticipation of issuing a revised Blue Book. In the White Paper, the Agency proposed changes to the EPA's methodology for estimating radiogenic cancers. The Agency expected to adopt the models and methodology recommended in BEIR VII, but believed that certain modifications and expansions were desirable or necessary for the EPA's purposes. EPA's Office of Radiation and Indoor Air (ORIA) requested the SAB to review the Agency's draft White Paper and provide advice

regarding the proposed approach to dose-response assessment of radionuclides. The EPA SAB/RAC prepared an advisory (EPA-SAB-08-006) (see http://yosemite.epa.gov/sab/sabproduct.nsf/FD9963E56C66E4FF852573E200493359/$File/EPA-SAB-08-006-unsigned.pdf). The SAB reviews responding to the above-cited EPA documents can be found on the EPA SAB Web site at http://www.epa.gov/sab.

The EPA's Office of Radiation and Indoor Air (ORIA) issued the draft of the revised Blue Book, entitled *"EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population"* (EPA, December 2008), and asked the SAB to review it. The draft document utilizes the advice contained in the BEIR VII, Phase 2 report, as well as the SAB's recently completed advisory for the White Paper described above (See also Appendix B for the Charge memo). The specific charge questions, given in Section 2.3 below, were provided to the SAB's augmented RAC with the completed draft document and asked for comments from the SAB's augmented RAC on application of the overall approach to cancer risk estimates for radionuclides. The document reviewed – the draft Blue Book -- includes the uncertainty estimates (from the 1999 document review by the SAB/RAC), and contains specific methodology applications for estimating the risks of radiogenic cancers for many organs and tissues.

2.2 Review Process and Acknowledgement

The SAB RAC met in a public teleconference on February 27, 2009, and conducted a public meeting on March 23, 24, and 25, 2009, for this review (see 74 Fed. Reg., 5935, February 3, 2009). An additional public teleconference took place on June 18, 2009 (see 74 Fed. Reg., 25529, May 28, 2009). These notices, the charge to the RAC and other supplemental information may be found at the SAB's Web site (http://www.sab.gov/sab). The quality review draft advisory dated August __, 2009, was forwarded to the Chartered SAB for its September 23, 2009, public teleconference meeting (see 74 Fed. Reg., _____, August __, 2009). This advisory also reflects suggested editorial changes from the Charter SAB.

The draft document *"EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population," December*, 2008 was well written. Presentations by the EPA staff to the RAC, as well as the public commentary, in the course of the public meetings were helpful. The EPA staff provided useful clarifications of its approach to preparation of the draft Blue Book, and conveyed information in response to questions by the augmented RAC that was necessary to perform this review. The EPA staff responded to all the RAC's requests and was forthcoming in explanations and clarifications.

2.3 EPA Charge to the Committee

Background

In 1994, the Environmental Protection Agency (EPA) published a report, referred to as the "Blue Book," which lays out EPA's current methodology for quantitatively estimating

radiogenic cancer risks. A follow-on report made minor adjustments to the previous estimates and presented a partial analysis of the uncertainties in the numerical estimates. Finally, the Agency published Federal Guidance Report 13 (FGR-13), which utilized the previously published cancer risk models, in conjunction with International Commission on Radiological Protection (ICRP) dosimetric models and U.S. usage patterns, to obtain cancer risk estimates for over 800 radionuclides, and for several exposure pathways. Prior to their publications, these three documents were first reviewed by the Science Advisory Board (SAB).

The National Research Council of the National Academies of Sciences released a report in 2006 on the health risks from exposure to low levels of ionizing radiation. Co-sponsored by the EPA and several other Federal agencies, *Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2* (BEIR VII) primarily addresses cancer and genetic risks from low doses of low-energy transfer (LET) radiation.

In a White Paper which was the subject of an SAB advisory review in 2006, the Agency outlined proposed changes to its methodology for estimating radiogenic cancers, based on the contents of BEIR VII and some ancillary information. For the most part, the Agency proposed adopting the models and methodology recommended in BEIR VII; however, in the White Paper the Agency also noted that certain modifications and expansions were desirable or necessary for their purposes.

The Agency accepted the recommendations of SAB, and is now requesting that the Agency's Science Advisory Board review the attached draft document entitled *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population,* dated December 2008, which was developed as a result of the previous White Paper advisory review (see U.S. EPA/ORIA. 2009 for reference to the specific request and charge questions to the SAB). The revised Blue Book will then serve as a basis for an updated version of FGR-13.

Specific Request

This draft document presents the scientific basis for new EPA estimates of cancer incidence and mortality risks due to low doses of ionizing radiation (IR) for the U.S. population. These estimates are based on available information, and for the most part, are calculated using models recommended in the National Research Council's BEIR VII Report.

1. As in BEIR VII, models are provided in the draft document for estimating lifetime risk as a function of age at exposure, gender, and cancer site, but a number of extensions and modifications to the BEIR VII approach have been implemented. First, BEIR VII focused on the risk from low-LET radiation only, whereas risks from higher LET radiations are also addressed here. Second, this document presents a slightly modified approach for combining BEIR VII models for projecting risks from Japanese A-bomb survivors to the U.S. population. Third, this document goes beyond BEIR VII in providing estimates of risk for kidney, skin, and bone cancers. Fourth, a modified method is employed for estimating breast cancer mortality risk, which corrects for temporal changes in breast cancer incidence and survival. Finally, quantitative estimates of risks for skin cancers and from prenatal exposures are included. Please comment on

the appropriateness of the following either not specified in BEIR VII or otherwise modified by EPA from BEIR VII:

a. Approaches described for extending risk estimates to radiations of different LETs - in particular, deriving site-specific risk estimates for alpha or low-energy electron and low-energy photon radiations based on models derived from the A-bomb survivors, who were primarily exposed to higher energy gamma rays (see Section 5).

b. EPA's adaptation of the BEIR VII weighted geometric mean approach for combining the EAR and ERR models for projecting risk from the LSS to the U.S. population (see Section 3.9).
c. Estimation of risks not specified in BEIR VII, including kidney, bone, and skin cancers, as well as for alpha particle irradiation of the liver (see Sections 3.3 and 5.1).
d. Method for calculating breast cancer mortality risk, accounting for the relatively long time from detection until death (see Section 3.10)
e. Approach for separating out nonfatal skin cancers and risks from prenatal exposures from the overall risk estimates (see Sections 3.3 and 6).

2. BEIR VII's approach to uncertainty is primarily based on data from the Life Span Study (LSS). The LSS provides a great deal of information on risks for many cancer sites; however precision is limited by errors in dosimetry and sampling errors. The sampling errors are often quite large for specific cancer types, and the uncertainties are even larger if one focuses on a specific gender, age at exposure, or time after exposure. Another important uncertainty is the transfer of site-specific cancer risk estimates to the U.S. population, based on results obtained on the LSS population, for sites with substantially different baseline incidence rate. Compared to BEIR VII, this document provides a somewhat altered and expanded analysis of the uncertainties in the cancer risk estimates.

Regarding the uncertainty analysis contained in Section 4,

a. Please comment on the adequacy of the approach to uncertainty analysis.
b. Are the distributions chosen for the various sources of uncertainty reasonable?

3. Please comment on the presentation of the following overall information and application of BEIR VII contained in the draft document:

a. Scientific defensibility and appropriateness of the models and assumptions employed for estimating risk.
b. Presentations of the calculations and results.
c. Regarding the document's intended purpose, the accuracy, balance, and level of detail of the scientific background material presented.

2.4 Blue Book Overview

The introductory Chapter 1 cites the earlier Blue Book (EPA 1994) and the BEIR VII Report (2006). The BEIR VII Report is the major source of information, but more recently published information has also been considered. Major sources of uncertainty are highlighted.

Chapter 2 presents the scientific basis for cancer risk. It briefly discusses biological mechanisms that lead to radiogenic carcinogenesis. It describes a modified linear no-threshold hypothesis and the extrapolation of low–LET risks from the measured results at relatively high doses to exposures at low doses and low dose rates. A Dose/Dose Rate Effectiveness Factor (DDREF) is introduced for calculating the risk from chronic low-dose and low-dose-rate exposure. Several effects that have been observed or proposed at low doses are discussed. The authors present a survey of the epidemiologic evidence for radiogenic cancer risk, notably the Life-span Study (LSS) of atomic bomb survivors at Hiroshima and Nagasaki, but also patients exposed to medical radiation. Epidemiological studies of cohorts exposed to low levels of radiation over extended periods, such as radiologists and nuclear workers, are cited.

The draft Blue Book presents revised estimates of cancer incidence and mortality risks due to low doses of ionizing radiation for the U.S. population. The risk estimates for solid cancers and leukemia, following exposure to low doses of low-LET radiations, are derived exclusively from preferred models developed by the BEIR VII committee. These models are applied to a stationary population based on survival rates in the U.S. to obtain an estimate of the lifetime attributable risk (LAR) per person-Gy for the U.S. population

The process for obtaining LAR is described in Chapter 3. It is based on a set of parameter values for the preferred ERR and EAR models in BEIR VII (Table 3-3). The EPA then uses a geometric weighting scheme to combine the results of both the ERR and EAR models to obtain a point estimate of the excess absolute risk, M (d,a,e), at an attained age a, following a single exposure to dose d, at age e. This is applied to the stationary population to obtain their “best estimate” of LAR.

Uncertainties in projections of LAR for low-LET radiations are described in Chapter 4. The entire focus of the uncertainty analysis is upon the calculation of LAR per-person-Gy for the U.S. population based on the data for the LSS. In effect, it is an independent assessment of uncertainty with a methodology quite different from that used to obtain point estimates in Chapter 3.

Risk of radiogenic cancer associated with high LET radiation, represented by alpha particles, is discussed in Chapter 5. Laboratory studies and human data are discussed. These include bone cancer associated with internal exposure to radium isotopes by injection (Radium-224) or ingestion (Radium-226, Radium-228), liver cancer associated with administration of diagnostic doses of Thorotrast to patients, plutonium intake by nuclear workers, and lung cancer among underground miners exposed to alpha particles from inhalation of radon gas (and radon-daughter particles) and among Russian nuclear workers at risk of inhaling plutonium particles. The risk is evaluated in terms of the RBE values based on contemporary data for alpha particles in specific organs or tissues.

Chapter 6 addresses cancer risk from prenatal exposure to radiation. Cancer incidence and mortality data from the LSS are not statistically significant with regard to cancer in adults associated with *in utero* exposure to x rays. Induction of childhood cancer due to fetal radiation exposure has been shown by Stewart et al. (1958); other case control studies have shown such risk (References in chapter 6, p.96), but the evidence is termed equivocal (Boyce and Miller 1999). The EPA here follows recommendations by the ICRP (2000) in adopting cancer incidence risks for solid tumors and leukemia, and cancer morality risk based on mortality rates for these occurrences.

In the very brief Chapter 7, application to calculating radionuclide risk coefficients is considered. The EPA will combine the revised excess cancer morbidity and mortality risk per Sv from this Blue Book with the latest ICRP dose models to revise the risk for each radionuclide per Bq intake or per unit exposure by external radiation. This information will be reported in a revision of Federal Guidance Report 13. The authors expect both increases and decreases, depending on the target organ.

3. RESPONSE TO CHARGE QUESTION 1: APPLICATION OF THE EXTENSIONS AND MODIFICATIONS TO THE BEIR VII APPROACH AS DESCRIBED IN THE DRAFT BLUE BOOK

3.1 Charge Question # 1: *As in BEIR VII, models are provided in the draft document for estimating risk as a function of age at exposure, age at risk,e gender, and cancer site, but a number of extensions and modifications to the BEIR VII approach have been implemented. First, BEIR VII focused on the risk from low-LET radiation only, whereas risks from higher LET radiations are also addressed here. Second, this document presents a slightly modified approach for combining BEIR VII models for projecting risks from Japanese A-bomb survivors to the U.S. population. Third, this document goes beyond BEIR VII in providing estimates of risk for certain other cancers. Fourth, a modified method is employed for estimating breast cancer mortality risk, which corrects for temporal changes in breast cancer incidence and survival. Finally, quantitative estimates of risks for skin cancers and from prenatal exposures are included. Please comment on the appropriateness of the following either not specified in BEIR VII or else otherwise modified by EPA from BEIR VII:*

a. Approaches described for extending risk estimates to radiations of different LETs - in particular, deriving site-specific risk estimates for alpha or low energy electron and photon radiations based on models derived from the A-bomb survivors, who were primarily exposed to higher energy gamma rays (see Section 5).

b. EPA's adaptation of the BEIR VII weighted geometric mean approach for combining the EAR and ERR models for projecting risk from the LSS to the U.S. population (see Section 3.9).

c. Estimation of risks not specified in BEIR VII, including kidney, bone, and skin cancers, as well as for alpha particle irradiation of the liver (see Sections 3.3 and 5.1).

d. Method for calculating breast cancer mortality risk, accounting for the relatively long time from detection until death (see Section 3.10)

e. Approach for separating out nonfatal skin cancers and risks from prenatal exposures from the overall risk estimates (see Sections 3.3 and 6).

3.2 Response to Charge Question # 1a

3.2.1 Alpha Particle Radiation

To derive risk estimates for site-specific alpha particle-induced cancers, EPA proposes to use the BEIR VII gamma-ray risk estimates, directly or with proposed modifications as necessary, after applying an RBE of 20. Exceptions to this general approach are proposed for 1) Leukemia for which an RBE of 2 will be applied to the BEIR VII-based gamma-ray estimate; 2) Liver cancer with an RBE of 40;

3) Lung cancer, for which EPA proposes continuing its use of models derived from BEIR VI to estimate the lung cancer risk from inhaled radon progeny; and
4) Bone cancer for which the alpha particle risk per Gy obtained by epidemiologic methods for patients exposed to ^{224}Ra by injection will be divided by an RBE of 10.

The RAC considers the general approach proposed by EPA for obtaining cancer risk estimates for alpha particle emitters using the RBE values that EPA proposes, to be reasonable and generally acceptable with the site-specific exceptions as identified. The choice of estimators for these site or type-specific cancers is discussed in response to question #1c.

3.2.2 Low-Energy Electron and Photon Radiations

Extensive discussion by RAC members regarding proposed changes to the RBE for low-energy electron and photon radiations identified the following items that should be addressed in the Blue Book:

- Was this recommended/suggested/implied in BEIR VII?
- Does ICRP, NCRP, UNSCEAR have similar recommendations?
- Does NIOSH (IREP) use an RBE > 1?
- Is the scientific rationale for this suitably mature at present (Health Protection Agency report)?
- What will be the reference source (1 MeV electrons and/or ^{60}Co)?
- Will this be restricted only to radionuclides with energies similar to ^{3}H?
- How will the "estimations" of "low energies" be determined in the case of mixed exposures (e.g., photons and beta particles)?
- What is the rationale for using cutoffs of specific energies, i.e., 1, 3 or 5 eV.
- Which radionuclides will be included and/or excluded?

In previous comments on the EPA White Paper (2006), RAC supported EPA's use of an RBE of 2 – 2.5 for photons of energies less than 30 keV and for ^{3}H beta particles (18.6 – 0 keV). In light of this and the current discussion, RAC recommends that EPA prepare a detailed argument/justification to support all proposed changes in the RBE values for specific ionizing radiations. The EPA should encourage a peer-reviewed publication that addresses these issues.

In particular, more detailed justifications are recommended for proposed changes to the RBE (to ~ 1.4) for photon energies used in diagnostic medical x rays. Given that medical radiation exposures make up the majority of the average US individual's annual radiation doses, the implications for individuals undergoing mammograms or CT scans might be significant in the long term. This justification is particularly important in light of the reference in the Blue Book to the Hunter and Muirhead (2009) study (page 95). Risk coefficients derived from studies of cohorts medically irradiated with x rays are in some cases lower than what has been berved for the A-bomb survivors.

3.3 Response to Charge Question # 1b

The site-specific risk estimates in BEIR VII were computed as a weighted geometric mean of ERR- and EAR-based lifetime attributable risk (LAR) estimates for the current (2000) US population. The EPA has proposed a method to compute an average excess risk function as a weighted geometric mean of age- (and age-at exposure) specific excess rates for the ERR and EAR models and then to apply this average excess rate function to a stationary US population to compute the LAR. The RAC was specifically asked about the decision to use an average excess rate function rather than averaging the ERR- and EAR-based LAR estimates. EPA staff explained during the meeting that the primary motivation for developing the average rate method was to insure additivity of age-specific risks.

The RAC considers that whether to use weighted geometric or arithmetic means to combine the ERR and EAR risk estimates is more important than whether to average excess rates and compute the LAR or to average LAR estimates. The RAC recommends that the LAR computations make use of the arithmetic mean even though this is a departure from the BEIR VII approach and even though the RAC endorsed the average rate method in its review of the White Paper (U.S. EPA/SAB 2008). The primary reason for this RAC recommendation is that the geometric mean implicitly gives more weight to the lower risk estimate whereas, when risks (or excess rates) are averaged by a weighted arithmetic mean, the choice of weights explicitly captures judgments about the relative importance of the ERR-and EAR-based risk estimates. Furthermore, because the use of arithmetic means for risk estimates insures additivity of the age-specific risk estimates, the RAC also recommends that the Blue Book present both ERR- and EAR-based LAR estimates and then compute the suggested risk estimate as a weighted arithmetic mean of the two estimates.

The RAC expects that the switch to arithmetic means and averaging LAR's will improve consistency between the suggested risk estimates and the central (mean/median) estimates from the uncertainty analysis. In any remaining cases where the central estimates are not the basis for risk estimates, EPA should explain the reason.

While this recommendation differs from the BEIR VII approach, for the reasons indicated above, the RAC considers that arithmetic means are preferable in dealing with radiation exposure transport. The BEIR VII report does not discuss this issue; geometric means may have been used primarily because they simplified the analytical uncertainty assessment carried out for BEIR VII. Because the EPA is using Bayesian Monte-Carlo methods to assess uncertainty, the complexity of the uncertainty evaluation is not affected by how the risks are combined.

Arithmetic means have been used for the current (and prior) ICRP recommendations. The Interactive Radio-epidemiology Program (IREP) also uses arithmetic means to combine relative-risk and excess- risk based estimates when computing probability of causation estimates. Both the 2000 and 2008 UNSCEAR reports (UNSCEAR 2008) present ERR- and EAR-based estimates, but do not combine them.

One question that arises if weighted arithmetic means are used in place of weighted geometric means concerns whether or not the EPA should change the site-specific ERR/EAR weights recommended by BEIR VII. The RAC does not believe that a change is needed because the BEIR VII members apparently were thinking in terms of linear (arithmetic) weights when they defined the weights used in their computations. The RAC does recommend that the report include a brief discussion of why, in most cases, greater weight is given to the ERR-based risks than to the EAR-based risks and of why this is not done in some cases (for example, lung and breast cancer).

The RAC agrees with the decision to use a stationary population rather than a census-based population in the LAR computations. The reasons for this change were cogently described in the EPA staff presentation to the RAC. The RAC recommends that this discussion be inserted in the Blue Book. This discussion (including presentation of gender-specific population pyramids (or age-adjusted rates for selected cancers) would be useful, with an indication, perhaps only for solid cancers as a group, to show how the switch from a census based population to a stationary population affects risk estimates.

3.4 Response to Charge Question # 1c

3.4.1 Kidney

In the absence of adequate epidemiological data for deriving a separate estimate for the risk of radiogenic kidney cancer following exposure to low LET, EPA's rationale for its proposed approach of using BEIR VII's residual cancers ERR model for kidney cancers, and with an adjustment factor for the EAR model, is reasonable. RAC supports this approach.

3.4.2 Bone

The RAC notes that its Advisory on the Agency Draft White Paper (2008) (section 5.7, page 19) supported the use of the human data to derive estimates of the bone cancer risk from ^{224}Ra. The data from the study of radium dial painters who were exposed to ^{226}Ra and ^{228}Ra were recommended to derive directly the bone cancer risk of these radionuclides. Although these approaches are outlined in the draft Blue Book (section 4.2.2, page 64), use of the radium dial painter data was proposed but apparently not pursued. The more detailed approach as proposed in section 5.1.2, pages 84-85, does not reflect attention to the Advisory's recommendation. The RAC now reiterates this recommendation because the nature of the exposures (chronic, lifetime) and their biokinetics are different for ^{226}Ra and ^{228}Ra than for ^{224}Ra.

In reconsidering the use of the radium dial painter data, the RAC recommends that EPA include the more recent analyses of the data for this population (Carnes et al. Radiat.Res.1997; Hoel and Carnes, 2004).

3.4.3 Skin (Fatal and NonFatal Nonmelanoma Cancers)

EPA proposes in draft Blue Book, pages 31-32, to deviate from its previous approach, (EPA 1994), based on ICRP recommendations (ICRP 1991b) for estimating the risk of radiation-

induced non-melanoma skin cancer (NMSC). This change is proposed to reflect the findings of more recent epidemiological analyses, changing disease patterns, and the conclusion that essentially all NMSCs induced by low-to moderate doses of ionizing radiation are of the basal cell type and non-fatal (Shore 2001; Preston et al 2007; Karagas et al1999; Ramsey, 2006 – as in the draft Blue Book).

EPA now proposes to use the BEIR VII model with age-specific baseline incidence rates to derive the ERR for nonfatal (incidence) radiation-induced NMSC. More recent estimates of mortality due to basal cell carcinoma in the general population (Lewis and Weinstock, 2004) will be used as baseline data in estimating the risk of fatal radiogenic NMSC. The NMSC risks for both incidence and mortality will be estimated for males and females separately and in combination (sex-averaged). EPA also will use the revised DDREF value of 1.5 (BEIR VII) to derive NMSC risk estimates in the low-dose range in place of the value 2 used previously.

The RAC considers the proposed updated approach for deriving risk estimates for fatal and nonfatal NMSC to be reasonable and acceptable.

3.4.4 Liver

The liver is recognized as a target organ for certain alpha-particle emitters. The relevance of the colloidal nature of the Thorotrast should be considered and how this might impact the radiogenic risks of liver cancer. Comparison of the liver cancer risk estimate for gamma radiation derived by BEIR VII from the LSS data with that obtained from the follow-up study of Danish Thorotrast patients suggested an RBE of 20 for alpha-particle radiation (Andersson et al. 1994). While recognizing the uncertainties inherent in both studies with respect to liver cancer and the value of this RBE, EPA initially proposed the use of 20 with the BEIR VII liver cancer risk estimate to derive an estimate for alpha particle-induced liver cancer (U.S. EPA/ORIA, 2006). RAC supported this approach for liver and certain other cancers that have been associated with alpha particle radiation (U.S. EPA/SAB, 2008) with the recommendation that any additional epidemiological data be taken into consideration.

Based on additional data from the follow-up study of German Thorotrast patients (Van Kaick et al. 1999) and a reanalysis of the Danish patient data (Leenhouts et al. 2002) with an empirical model and a lifetime risk projection, EPA has revised its proposal to use a scaled version of the BEIR VII model. The EPA now will use BEIR VII's low-LET age and gender-specific liver cancer risk estimates and an RBE of 40 to provide risk estimates for alpha-particle induced liver cancer at environmental low doses. The RAC considers this approach reasonable, and the use of an RBE of 40 as appropriate. EPA may wish to distinguish among the various types of liver cancers; for example, are the LLS and Thorotrast cancers identical?

3.4.5 Lung

The draft Blue Book adopts an RBE of 20 for lung cancer by alpha-particle emitters other than radon, for which BEIR VI models are used. A separate risk model for radon is the best approach as outlined in the draft Blue Book. The human epidemiological evidence for other inhaled alpha-particle emitters comes primarily from the Mayak studies, because other studies do not have significant power to estimate risks. As noted in the draft Blue Book (U.S. EPA/ORIA.

2008), the Mayak studies are in an early stage, but several reports are available. The lung cancer risk estimates reported by the two most recent Mayak reports (Jacob et al 2007, and Sokolnikov et al 2008) were consistent with an RBE of 20 for males and 10 for females (Kreisheimer et al. 2000

Given the preliminary nature of the Mayak studies, EPA proposes to use an RBE of 20 for both males and females. This approach is reasonable. The same value of 20 has been recommended recently by the ICRP (2003, 2005). Some of the RBE's observed in animal studies are consistent with a value of 20 or above (Gilbert at al 1997; Hahn et al 1999; Lundgren et al 1995, 1996, 1997; Muggenburg et al 1996, 2008) but other animal studies suggest a much lower RBE (Priest et al 2006). Significantly elevated risks for radiogenic lung tumors in the animal studies are generally observed at 1 Gy, well above the low-dose range.

3.4.6 Leukemia

The draft Blue Book recommends an RBE of 2 for alpha-particle-induced leukemia based on human epidemiological studies of low doses of ^{224}Ra. This is a change from a value of 1 used in past EPA reports. The value is reasonable for calculating doses to the marrow by the ICRP approach, but is uncertain because of the dosimetry and different temporal patterns for the appearance of the leukemias between the LSS and the ^{224}Ra study. The animal studies do not have sufficient power to estimate leukemia risks.

3.5 Response to Charge Question # 1d

BEIR VII computed breast cancer mortality risk estimates by scaling age-specific incidence risks for the ratio of the (age-specific) mortality-to-incidence rate ratios. EPA proposes replacing this simple ratio by a factor that allows for the relative survival of breast cancer patients. The data presented to the RAC by EPA staff strongly suggest that the modified method leads to more realistic breast cancer mortality risk estimates. The RAC believes that EPA's method is an improvement over that used by BEIR VII because the relative survival of breast cancer patients is high and the excess risk estimates, including those derived by application of ERR estimates, used in the LAR computations increase with attained age. The EPA should consider using a similar approach in computing mortality risks for other types of cancer, particularly those, such as prostate and uterus, that have high relative survival rates.

3.6 Response to Charge Question # 1e

3.6.1 Nonfatal Skin Cancer

As noted in the response to Question #1c with regard to Skin (Fatal and nonfatal cancers), the RAC supports EPA's proposal to update its approach for estimating the risks of radiation-induced NMSC in the light of more recent epidemiological data. In particular, RAC supports Shore's conclusion that essentially all NMSC induced by ionizing radiation in the low to moderate dose range are of the basal cell type (BCC) with a very low mortality rate (Shore 2001), and hence, EPA's proposal to derive risk estimates for incidence and mortality due to radiation-induced NMSC from data for BCC.

The RAC supports EPA's decision, in keeping with usual practice, not to include NMSC risk estimates in estimating the estimates of total radiogenic cancer risk (see Tables in the draft Blue Book, sections 3 and 4).

3.6.2 Prenatal Cancer Risk

Estimation of cancer risks from prenatal radiation in the draft Blue Book is appropriately based on the literature. Prenatal radiation exposure has been shown in some studies to be causally associated with increases in childhood cancers and, in the LSS, with increases in adult cancers.

In the draft Blue Book, EPA adopts a childhood cancer risk value of 0.06 Gy^{-1} (absolute risk for dying of leukemia by age 16) for prenatal exposure that was suggested by Doll and Wakeford (1997), and adopted by the ICRP (2000). This value has been controversial because other studies have been equivocal (Boice and Miller 1999), but the value is reasonable based on reviews of the evidence. This evidence is from medical x-ray doses and energies (80 kVp); the risk coefficient would be adjusted to 0.04 Gy^{-1} if the RBE of 1.4 for diagnostic medical x rays is adopted.

For estimating the risks of adult cancers among populations exposed *in utero,* EPA proposes adopting the cancer risk models in draft Blue Book section 3 with age set to 0. This approach is based on an analysis of A-bomb survivors exposed *in utero* that found a lower risk than those who were irradiated as young children, but the difference is not statistically significant (Preston et al 2008). The RAC considers this a reasonable approach.

Caution must be expressed because some spontaneous abortions may have occurred in women who received the higher doses in the periods immediately after the A-bombs. These were unaccounted for in the LSS and would lower the risk estimates. This possible problem should be mentioned by EPA as an additional source of uncertainty for prenatal exposure effects.

TBA – a comment re inclusion risk (or not) in the overall estimate of cancer risk of the risk estimates for childhood and adult cancers among populations exposed in utero.

4. RESPONSE TO CHARGE QUESTION 2: THE UNCERTAINTY ANALYSIS

4.1 Charge Question # 2: *BEIR VII's approach to uncertainty is primarily based on data from the Life Span Study (LSS). The LSS provides a great deal of information on risks for many cancer sites; however precision is limited by errors in dosimetry and sampling errors. The sampling errors are often quite large for specific cancer types, and the uncertainties are even larger if one focuses on a specific gender, age at exposure, or time after exposure. Another important uncertainty is the transfer of site-specific cancer risk estimates to the U.S. population, based on results obtained on the LSS population, for sites with substantially different baseline incidence rate. Compared to BEIR VII, this document provides a somewhat altered and expanded analysis of the uncertainties in the cancer risk estimates.*

Regarding the uncertainty analysis contained in Section 4,

c. Please comment on the adequacy of the approach to uncertainty analysis.
d. Are the distributions chosen for the various sources of uncertainty reasonable?

4.2 Response to Charge Question # 2a

The approach to obtaining quantitative estimates of uncertainty is reasonable and comprehensive. The RAC, however, has identified specific issues relating to the uncertainty analysis that should be addressed in order to clarify assumptions and to provide additional information for the readers of the draft Blue Book, and these are described below.

4.2.1 General Comments

The methods used for the full uncertainty analysis of stomach, colon, liver, lung, and bladder cancer are based on analysis of the data for the Japanese atomic bomb survivors, the LSS. The LAR is a complex function of parameters that can be classified into three types. Type (I) are the risk estimates obtained from models using parameters derived from the LSS data. Type (II) are other parameters, such as RBE, DDREF, and population transfer, about which little or no direct information comes from the LSS data. Type (III) is the age distribution obtained from a hypothetical (stationary) population that mimics the US population. The goal of the uncertainty analysis in the EPA draft Blue Book is to combine sampling variation in the estimates for Type (I) parameters with uncertainties in Type (II) parameters in order to provide an overall uncertainty estimate for the LAR that is calculated either separately for individual tumor types or for groupings of tumors (e.g. all solid tumors, leukemia).

A Bayesian analysis has been adopted by the EPA. It provides a consistent framework for the treatment of unknown parameters as random variables and a formal method for updating initial prior distributions for these random parameters with the information contained in the LSS data about the parameters of Type (I). Thus the Bayesian nature of the uncertainty analysis rests

upon a somewhat different statistical basis than a "frequentist" approach that yields the "best estimates" of LAR for these cancers. It is not surprising that the LAR uncertainty bounds from the Bayesian analysis are not completely symmetric around the best estimate.

In addition to the mere fact that EPA's uncertainty analysis of LAR is Bayesian in nature, the Bayesian analysis for stomach, colon, etc., actually is a joint analysis of these cancers and combines information about the linear excess relative risk parameters across these cancer types. It estimates a common mean (but separately by sex) and a common variance in the distribution of these risk parameters. Doing this should have the useful property of reducing the uncertainty in the posterior distribution of these risk estimates especially for rarer cancers where the information in the LSS likelihood is not large.

Because all Type (I) and Type (II) parameters are regarded as random variables, the LAR itself is treated as a random variable that is a function of these random variables in the uncertainty analysis. While this general framework is sound, it is complicated, especially given the need to provide prior distributions for all Type (I) and Type (II) parameters. Because of the large amount of direct data from the LSS related to incidence and survival, the selection of prior distributions for Type (I) parameters does not have a very strong effect on the final "posterior" estimates of these parameters. However, prior distributions specified for Type (II) parameters tend to dominate their posterior distributions because little or no information about these parameters is in the LSS data.

4.2.2 Specific Comments

The draft Blue Book should clearly state and justify why one method is used to obtain a point estimate of LAR and another method based on different assumptions is used for the uncertainty analysis. The Bayesian approach provides a posterior density function for LAR that could be used to obtain a "best estimate" (i.e. mean or median) as well as confidence limits for a quantitative description of uncertainty. Thus, a Bayesian approach could provide a consistent value for both the best estimate and uncertainty interval, instead of a frequentist approach for the best estimate and then Bayesian methods to estimate the confidence interval.

Presumably, EPA used separate approaches to obtain a best estimate and confidence intervals partly because the best estimate of a LAR for a specific cancer site does not impose the constraint that the risk estimates for each cancer be similar. Thus, because such risk estimates are not known *a priori* to be similar, it may be scientifically more sensible to use completely different analyses of each cancer subtype to give the best estimate, even if an assumption of commonality is necessary and reasonable to impose when evaluating uncertainty, especially for relatively rare cancers.

An additional reason why Bayesian analysis might not be applied to generating the best point estimates is that Bayesian estimates depend greatly on the details of the priors used for Type II parameters, which are inherently subjective. One also needs to utilize inherently subjective choices to develop the point estimate. However, the technical details and software (WinBUGS) used for the Bayesian analysis are quite delicate. Although WinBUGS (Lunn et al 2000) is preferred for many Bayesian applications, convergence issues often arise. The Markov

Chain methodology can be demanding. For example, minor changes in starting values used in the simulations can have a large effect on the results. In general, the RAC is sympathetic to the process of using specific assumptions for Type (II) parameters to produce the point estimates, but then allowing these to range widely when the uncertainty intervals are computed.

In addition to concerns relating to prior distributions, the RAC notes an overall lack of clarity concerning the likelihood function for the LSS data. The likelihood function for Poisson regression analysis of grouped survival data may not be very familiar even to readers relatively knowledgeable in statistics and should be described carefully. Moreover, because for the cancers listed above (stomach, colon, etc.), a joint analysis is being performed (where tables of person years and events are given for more than one outcome), the legitimacy of multiplying the likelihoods for each outcome together should be affirmed, even though the same "denominator" values (person years) are being used in each table.

The current description of LARs and corresponding uncertainty intervals are not sufficiently detailed. No indication is given as to which parameters, either Type (I) or Type (II), are the most influential in controlling the uncertainty intervals for LAR.

The RAC suggests that EPA create a table depicting the relative contribution of each source of uncertainty to the total uncertainty for each LAR (i.e., site-specific and overall). The sources of uncertainty include (1) incidence data (where 'incidence' includes both background and radiogenic incidence), (2) DDREF, (3) risk transport model, and (4) "other" (EPA) sources, including age and time dependence, errors in dosimetry, and diagnostic misclassification. The relative contribution could be expressed as a percent or as the squared correlation between LAR uncertainty and each source of uncertainty, i.e. the correlations, between the random parameters and the LAR, in the Monte-Carlo simulations used to evaluate the posterior distributions of these quantities.

Given the delicate nature of the Monte Carlo Markov Chain calculations, verification of the uncertainty intervals so obtained by a perturbation approach would be beneficial as a means of extending the analysis. The RAC suggests the following: Use the results of the current approach to the uncertainty analysis to identify one or two key parameters for each point estimate (where 'key' means most contributory to overall uncertainty). Then, in the model used to generate the point estimate, vary the key parameters over their range in a parametric sensitivity analysis (perturbation analysis) to generate a range of resulting risk estimates. This should indicate the operational range of the point estimate. In this way, one can verify whether of not the results of the current uncertainty are appropriate for a given point estimate, and observe the width of confidence intervals for that point estimate.

As a general methodological comment on the usefulness of the posterior densities resulting from a Bayesian approach, the RAC suggests considering in future risk predictions the concept of the predictive density (**REFERENCE NEEDED HERE**). It is well established in other applications of survival analysis e.g. reliability analysis and takes all remaining parameter uncertainty into account for the calculation of predicted quantities. Increased computing power and advances in numerical integration (e.g., Quasi Monte Carlo Methods) make this feasible if

the dimensionality of the integrand is not too high (e.g. < 10). (c.f. William M. Bolstad, Introduction to Bayesian Statistics, 2nd ed., John Wiley & Sons, Hoboken NJ, 2007).

When comparing the results of the draft Blue Book to previous estimates published in FGR 13, the authors stated that "The overall increase in LAR is not due to changes in the basic risk models," but that; "…the increase in results is largely attributable to the use of the more recent SEER incidence data as a primary basis for calculating incidence rates." To what extent is this reflected in the distributions for sources of uncertainty in Table 4.2?

The prior distributions for Type (I) parameters in the ERR and EAR risk models are formed with numerical distributions of the parameters themselves from Table 4.1. Uncertainty of the Type (II) parameters is based on the product of a constant (i.e. DDREF =1.5) and a random multiplicative factor [LN (GM=1, GSD=1.35)]. What is the reason for the two different approaches? It seems that a multiplicative factor that is log-normally distributed would lead to a bias unless the mean value for this multiplicative factor is equal to 1.0. This is not the case for LN (0.95, 1.1) or LN (1.1, 1.1).

4.2.3 Additional Comments on Risk Transfer

For many reasons, risk due to radiation exposure may differ between populations. We are only beginning to learn about such important issues as population differences in genetic susceptibility to cancer and how such genetic differences would interact with radiation. Throughout the draft Blue Book, EPA assumes that if the background rate of a particular cancer is similar in Japan and the US (or in specific Japanese and US subpopulations), then the excess risk of cancer due to radiation will also be similar. In reality, this may be a simplification and as we learn more about genes (or environmental exposures other than radiation) that interact with radiation, we may find that many of them differ in gene or exposure frequency between Japanese and US populations. Nevertheless, a reasonable assumption, given today's (lack of) knowledge, is that cancers with similar baseline rates will have similar response to radiation exposure in the two populations. This forms the basis for transferring risk models and the associated LAR calculations from the Japanese to US populations.

For cancers with widely different baseline risks (e.g., stomach or prostate cancer), between the Japan and US populations, the choice of an ERR or EAR model can make a large difference in the LAR when applying the Japanese risk estimates to the US data. One key Type (II) parameter is the weighting parameter which interpolates between the excess absolute risk (EAR) and excess relative risk (ERR) models. The LSS data provides no information about whether EAR or ERR models are more reasonable because both these models provide equivalent descriptions of the LSS data.

The RAC in its response to charge question 1b, above, indicates a preference for an arithmetic rather than geometric mean-based method of interpolation between the LARs produced by transferring the EAR or the ERR model to the US. A key issue is the weighting of these two models. The general sense of the RAC is that weighting should emphasize ERR models more than EAR models: except for outcomes (e.g., breast cancer) with enough relevant data outside the LSS population to indicate that the EAR models transfer more accurately. This

emphasis does appear in the point estimation process (which to the extent that it follows BEIR-VII places weight of 0.7 on the ERR and 0.3 on the EAR results). This emphasis seems to be based on observations that, over tumor sites with different frequency of background occurrence, and sometimes also over different strains of experimental animals, ERR parameters tend to be more similar than EAR parameters (Preston et al 2007).

While point estimates do emphasize transference of the ERR models, the uncertainty analysis gives only a slight overall bias in favor of ERR compared to EAR models in the MCMC calculations. The RAC suggests placing additional weight on ERR models overall in the uncertainty analysis. The tendency for the EAR models to be stressed more in the uncertainty analysis than in the point estimation may underlie why in Table 3.11 the point estimates for stomach cancer (31 cases per 10,000 person Gy) are so far from the midpoint of the uncertainty interval (9-280 cases per 10,000 person Gy).

4.3 Response to Charge Question # 2b

The RAC did not identify any specific issue with the selection of distributions used to characterize uncertainty in parameters for used in the models to obtain LAR**.** However, the committee recommends that the EPA clarify the reasoning behind the selection of the subjective priors used in the analysis (e.g., in Table 4-1). This would also increase transparency of the draft Blue Book and facilitate future scrutiny and verification of the assumptions used in the uncertainty analysis.

5. RESPONSE TO CHARGE QUESTION 3: COMMENTS ON PRESENTATION OF OVERALL INFORMATION AND APPLICATION OF BEIR VII IN THE DRAFT BLUE BOOK

5.1 Charge Question 3*: Please comment on the presentation of the following overall information and application of BEIR VII contained in the draft document:*

a. Scientific defensibility and appropriateness of the models and assumptions employed for estimating risk.
b. Presentations of the calculations and results.
c. Regarding the document's intended purpose, the accuracy, balance, and level of detail of the scientific background material presented.

5.2 Response to Charge Question # 3a

The RAC finds that the draft Blue Book presents models and assumptions for estimating risk that are broadly applicable and scientifically defensible. It is part of a fine effort to prepare a series of steps that apply various models – especially those by BEIR VII for low-LET radiation -- as a basis for radiation protection regulations. Also commendable is the related EPA effort to improve BEIR VII models and to apply other models for cancer risks that BEIR VII does not address. The RAC suggests the following topics for consideration in improving the draft Blue Book.

5.2.1 Consideration of NonCancer Mortality

The current report focuses on cancer mortality and incidence, and does not address the possibility of radiation-related noncancer mortality. Noncancer mortality, particularly mortality from cardiovascular disease, has been linked with exposure to high therapeutic radiation doses (BEIR VII), but it is not clear whether such effects are found at lower doses. Mortality from most broad noncancer disease categories has been found to be related to radiation dose in the LSS cohort (Preston et al., 2003). However, because the identified radiation risks were small compared to baseline risks, it was not possible to evaluate age effects or the shape of the dose-response function with any precision. For example, it was not possible to distinguish a linear dose-response from a dose-response with a threshold as high as 0.5 Gy. Indications also exist of radiation-associated increases in diseases of the circulatory system among nuclear workers in the United Kingdom (McGeoghegan et al., 2008).

Lifetime risk estimates for radiation-related noncancer mortality for the LSS cohort are uncertain and range from zero to levels that approach those for cancer mortality estimates (Preston et al 2003). Due to the large uncertainties in the possible magnitude, or even existence, of increased noncancer disease risk at low doses, the EPA's decision not to provide lifetime risk estimates for noncancer mortality is reasonable. The RAC recommends that noncancer mortality

be mentioned as a possible effect of radiation exposure even at low doses, and that the reasons for not providing risk estimates for this endpoint at the present time be stated.

5.2.2 Information from ICRP and UNSCEAR Reports

Since the publication of BEIR VII, both ICRP (*3*) and UNSCEAR (*4*) have published reports that include lifetime risk estimates for radiation-related cancers. ICRP developed estimates for a world population defined as an average of risks for hypothetical Euro-American and Asian populations, whereas UNSCEAR developed estimates for several different countries, including the United States**.** The RAC recommends that the EPA add a brief description of the methods used in the ICRP and UNSCEAR reports and a comparison with those that are being used by EPA. Tables showing comparisons of the EPA estimates with relevant estimates from ICRP and from UNSCEAR would be a desirable addition to the Blue Book.

5.2.3 Radiogenic Thyroid Cancer

The RAC reserves comment on EPA's proposed approach to estimating the risk of radiogenic thyroid cancer. Information in the draft Blue Book is limited (page 26), and should be enhanced on the basis of the recently published NCRP Report #159 on this topic (**REFERENCE NEEDED HERE**). Thyroid cancer risk estimates are important to radiation protection and NCRP is considering recent epidemiological and related data that were not available to BEIR VII.

5.3 Response to Charge Question # 3b

The RAC found the presentation of calculations and results in the draft Blue Book to be competent and comprehensible.

5.3.1 Table 4.2 Clarification

The RAC recommends that, in Table 4-2 on sources of uncertainty, a column listing references for the source of the distribution parameters be added, and that these be discussed in the text. It also recommends elimination of reporting the same values of lifetime risk estimates of cancer incidence or mortality which are in several tables.

5.3.2 Enhanced Topical Organization and Content

The RAC recommends that at the beginning of the document, EPA clearly states the intended purpose and application of the document, and anticipating the contents of the subsequent documents based on the Blue Book. The organization of the Blue Book can be improved by pulling together some scattered topics. For example, in Section 3.3 (draft Blue Book pages 29 – 32), risk models for cancers not specified by BEIR VII (kidney, bone, NMSC etc.) are discussed and conclusions presented, but estimating cancer risks for these organs is discussed in detail in Section 5.(pages 84 -88). The RAC found that some of the more detailed

explanations and examples provided in the materials orally presented on March 23, 2009, to clarify the Blue Book contents greatly and suggests that they be included in the Blue Book.

5.3.3 SEER Data Clarification

The RAC suggests that additional information on the updated surveillance, epidemiology and end results (SEER) would be helpful. The statement on page 55 that increased LAR estimates (compared to those of FGR 13) are "largely attributable to the use of more recent SEER incidence [rates]" is confusing. Is the main point that FGR 13 made use of (poorly) approximated incidence rates computed as lethality-adjusted mortality risks but that the new estimates are based on actual age-specific incidence rates?

5.3.4 Application of DDREF

The RAC recommends that tables with LAR estimates indicate whether the estimates include a DDREF adjustment.

5.4 Response to Charge Question # 3c

The RAC finds that the draft Blue Book, on the whole, presents the scientific background material with adequate accuracy, balance, and level of detail, but suggests the following improvements in use of information from low-dose protracted exposures and consideration of error.

5.4.1 Low-Dose Protracted Exposure.

The RAC realizes that much of the draft Blue Book relies on BEIR VII risk estimates based on LSS data, but better balance would be achieved by comparing and discussing differences in risk estimates between the revised EPA estimates and risk estimates from the many international studies of nuclear workers. The EPA's primary concern is with the health effects of low-level, protracted radiation exposure. The EPA also acknowledges that the transfer of risk from an acute, high-level exposure in a Japanese population to the U.S. population is problematic.

Data on health effects at relatively low level protracted exposures are available from the 15-country radiation worker study (Cardis et al 2007; Cardis et al 2008), the analysis of UK's National Registry of Radiation Workers (Muirhead et al. 2009) the study of Mayak workers (Khokhryakov et al 2000), the study of U.S. radiation technologists (Mohan et al 2003; Sigurdson et al 2003; Yoshinaga et al. 2004), and studies of populations who were irradiated in medical diagnostic procedures (UNSCEAR 2006). The overwhelming majority of these workers received doses less than 100 mGy, i.e., in the dose range of interest.

5.4.2 Balanced Consideration of Sources of Error

The RAC encourages evaluation of the relative importance of the impact of sources of the various errors, including those currently not considered in the development of the uncertainty distributions, with focus on examining the most important contributors. As one example, in the transfer of risk between the LSS cohort and the U.S., what will be the impact on the uncertainty distribution if the true transfer model falls outside the limits defined by the purely additive and purely multiplicative risk transfer?

5.4.3 Cancer Subtypes

The RAC encourages expanding the discussion of issues related to lympho-hematopoietic cancers, for example: a) comments on the recent literature suggesting that Chronic Lymphocytic Leukemia (CLL) may be a radiogenic cancer (Linet et al. 2007; Schubauer-Berigan 2007; and Silver et al 2007), and appropriate references contained within; b) the reasons for not developing risk estimates for leukemia subtypes; and c) why risk estimates have not been presented for non-Hodgkin's lymphoma or multiple myeloma.

5.4.4 Holistic View of Stepwise EPA Path to FGR 13 Revision

The RAC recommends that EPA include specific information concerning the anticipated radionuclide risk coefficient values in the revised FGR 13, based on currently available dosimetric models. The presentation in the 1994 Blue Book, Tables A4a and A4b are an example. This improvement of the vague presentation currently in chapter 7 is important to both professionals and the public who wish to evaluate the combined impact of revised cancer risk projections and dosimetric models. Any satisfaction or concern with respect to the results in the Blue Book is premature without considering FGR 13 values.

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APPENDIX A – EDITORIAL COMMENTS

p.6: Insert acronyms:
UI Uncertainty interval
ICD ? (used on p.23)

p. 7, paragraph 2: This should mention the provision of estimates for alpha-emitters, X-rays etc. Also, kidney cancer should be added to the list in the 3rd sentence.

p. 7, paragraph 4: Sentence "Nevertheless … time after exposure." This is true, but for most cancers the estimates are more precise than those from any other study. This point might be worked into the paragraph. Another limitation that might be mentioned is the relevance for low dose rate exposure.

p.16, Section 2.1.5, line 2: Replace 'new' by 'recently observed'.

p. 20, 1st full paragraph: The study of British radiologists by Berrington et al. (Br. J. of Radiology 2001) might also be cited.

p. 20, 2nd full paragraph: An important paper on workers that needs to be cited is the recent update of the study of NRRW British nuclear workers (Muirhead et al. Brit. J. Cancer, 2009). The most important limitations (in my opinion) are not mentioned. These are lack of statistical power (imprecise risk estimates) and vulnerability to confounding when studying small risks. There are also more recent Chernobyl papers that might be cited including 2 papers on thyroid cancer (Cardis et al. JNCI 2005; Tronko et al. JNCI 2006) and 2 papers on leukemia incidence (Romanenko et al. Radiat. Res. 2008; Kesminiene et al. Radiat. Res. 2008).

p. 21, line 1: Kidney cancer should be added here.

p. 23, last 2 lines: Suggest revising as following: "… the BEIR VII committee found that the ERR per Gy decreased by about 25% per decade of age at exposure (for ages under 30) in the model …

p. 25, Table 3-2: For thyroid cancer, attained age (*a*) id not an effect modifier. The Ron et al. pooled analysis should also be cited. For leukemia, the ERR and EAR were *linear*-quadratic functions of dose.

p. 27, "Breast" paragraph: It would be helpful to indicate briefly the rationale for using only an EAR model for this site.

p.27, Table 3-3: Last letter in heading should be Greek eta, not 'H'.

p.28, Fig.3-2 and others: Always show units along axes.

p.41, Section 3.9.2: insert period after '9'.

p. 43: Line just below equation 3-21. The inequality is incorrect. When one multiplies the expression in 3-21 by $M^{(A)} - M^{(R)}$, the direction of the inequality will change when $M^{(A)} - M^{(R)}$ is negative.

p. 43, last paragraph: The wording here is confusing. Equation (3-20) seems to *assume* the $M^{(true)}$ that is between the EAR and ERR estimates.

p. 55, 3rd sentence: BEIR VII accounted for uncertainty in the age parameters for the all solid cancer estimate.

p.57, Table 3-13: Do the 90% UI values refer to Kidney or to combined Residual + kidney as in Table 3-11?

p. 59, paragraph 2: Another important difference is the approach to transport.

p. 62 ff: If there is sharing of the main effect parameters, I would think there should be sharing of the age parameters as well. Also, there should probably be allowance for correlation of the age at exposure and attained age parameters. (I have no idea what the impact of the changes might be.)

p.63, Table 4-1: Replace 2nd parameter heading (9it is the same as the 1st).

p.77, Table 4-4b: Insert 'age' in heading before '15'.

p.83, Table 4-5: Although heading says '95% uncertainty intervals', the values are similar to the 90% uncertainty intervals of Table 3-11. Check.

p. 88, 1st full paragraph: The more recent Sokolnikov et al. paper should also be cited here.

p. 90, 1st full paragraph: I suggest providing confidence intervals for these estimates to remind readers of the considerable uncertainty. This comment also applies to many other estimates presented in the report.

p. 90, 2nd full paragraph: We argued in the Gilbert et al. 2004 paper that the estimates of the ERR per Gy from plutonium and from radon were fairly comparable. You might want to check this paper (beginning 2nd column on p. 514).

APPENDIX B –ACRONYMS

(NOTE: Contains acronyms relevant specifically to the Blue Book Review. Please complete missing items as appropriate. - - - KJK)

A	Atomic
AM	Arithmetic Mean
BCC	Basal Cell Carcinoma
BEIR	Biological Effects of Ionizing Radiation (Pertains to committees of the Board of Radiation Effects, National Research Council of the National Academy (now the National Academies'), charged with assessing the Biological Effects of Ionizing Radiation
BEIR VII	The report entitled "*Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII – Phase 2"* published (2006) by the Committee to Assess Health Risks from Exposure to Low levels of Ionizing Radiation of the Board on Radiation Effects Research, national Research Council of the National Academies
Bq	Becquerel
CLL	Chronic Lymphocytic Leukemia
Co	Chemical symbol for Cobalt (^{60}Co isotope)
CT scan	Computed Tomography (CT or CAT Scan)
DDREF	Dose and Dose-Rate Effectiveness Factor
EAR	Excess Absolute Risk
EPA	Environmental Protection Agency (U.S. EPA)
ERR	Excess Relative Risk
eV	Electron Volts
FGR	Federal Guidance Report
GM	Geometric Mean
GSD	Geometric Standard Deviation (?)
Gy	Gray, SI unit of radiation absorbed dose (1 Gy is equivalent to 100 rad in traditional units)
H	Chemical symbol for Hydrogen (^{3}H isotope)
ICRP	International Commission on Radiological Protection
I	Chemical Symbol for Iodine (^{131}I isotope)
IR	Ionizing Radiation
IREP	Interactive Radio-epidemiology Program
k	Kilo (thousands)
kVp	Kilo Volts (p ?)
LAR	Lifetime Attributable Risk
LET	Linear Energy Transfer
LN	Linear Non-Threshold (also LNT)
LSS	Life-Span Study
mGY	Milli (one Thousandth) Gray
MCMC	Markov Chain Monte Carlo methods
Me	???
NAS	National Academy of Sciences

NCRP	National Council on Radiation Protection and Measurements
NIOSH	National Institute for Occupational Safety and Health
NMSC	Non-Melanoma Skin Cancer
NRC	National Research Council
OAR	Office of Air and Radiation (U.S. EPA/OAR)
ORIA	Office of Radiation and Indoor Air (U.S. EPA/OAR/ORIA)
Ra	Chemical symbol for Radium (Isotopes include ^{224}Ra, ^{226} Ra, ^{228}Ra, and ^{236}Ra)
RAC	Radiation Advisory Committee ((U.S. EPA/SAB/RAC)
RBE	Relative Biological Effectiveness
SAB	Science Advisory Board (U.S. EPA/SAB)
SEER	Surveillance, Epidemiology and End Results
Type I	Decision error (in this case on risk estimates). A decision error occurs when the *null hypothesis* is rejected when it is true. The probability of making a Type I decision error in called *alpha*.
Type II	Decision error (in this case on risk estimates). A decision error that occurs when the *null hypothesis* is accepted when it is false. The probability of making a Type II decision error is called *beta*.
Type III	Decision error (in this case on the age distribution)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
US	United States of America – used interchangeably with USA
V	(???)
WinBUGS	Windows (for Microsoft windows programs) for Bayesian inference Using Gibbs Sampling analysis software
X-ray	

End of Document