UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

- - - Date To Be Added - - -
Quality Review Draft of August 20, 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 EPA Office of Radiation and Indoor Air (ORIA) outlines proposed changes in methodologies for estimating radiogenic cancer risk, and gives examples of risk estimates for individual radiogenic cancers that it derived. Most methodologies were recommended in the National Research Council BEIR VII Report (NAS/NRC 2006), sponsored by EPA and other federal agencies.

The draft Blue Book is impressively researched, based on carefully considered concepts, and well written. The following are the responses by RAC to the sets of questions asked by EPA/ORIA staff on the three listed topics.

1) Appropriateness of models not taken directly from BEIR VII

The RAC recommends that for low-energy beta particles, gamma rays, and x rays, because insufficient information for selecting relative biological effectiveness (RBE) values has been presented, the EPA staff encourage publication in a peer-reviewed journal of such information for review by the scientific community and then apply RBE values based on this evaluation. The RAC agrees with the EPA approach for estimating risks from exposure to radionuclides that emit alpha particles with their much greater linear energy transfer (LET) and associated RBE.

The RAC recommends -- in contrast to BEIR VII -- use of a weighted arithmetic mean for each set of excess absolute risk (EAR) values and excess relative risk (ERR) values for 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 applying either the arithmetic or geometric mean, is that the arithmetic mean results from linear addition and averaging of excess risk data and equally emphasizes higher and lower values. The choice of weighting factor then explicitly captures judgments about the relative importance of the ERR- and EAR-based risk estimates.

The RAC agrees with the approaches proposed by the EPA to derive risk estimates for solid cancers not specified in BEIR VII (kidney, skin), or for cancers associated with exposure to alpha-particle emitters (lung, liver), and also agrees with the EPA approach for nonmelanoma skin cancer and prenatal exposure. ***The RAC recommends, for bone cancer, that the EPA reconsider utilizing the radium data for the dial painter cohort (as asserted in the Blue Book, but not done) and, most importantly, apply recently published analyses of the data.***

The RAC compliments the EPA on developing an improved model that considers the survival rate of breast cancer patients. It suggests that the EPA apply this model to other cancers with high rates of survival.

2) Adequacy and reasonableness of the uncertainty analysis by the EPA

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 make Bayesian uncertainty analysis as consistent as possible with the point estimate of risk. The EPA should justify use of two distinct approaches to obtain, respectively, the confidence interval and the best estimate value.

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

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

3) Validity of scientific defensibility, presentation, and completeness

The Blue Book is scientifically defensible and appropriate. ***The RAC recommends that the EPA enhance content by reporting further information from (1) studies of noncancer mortality; (2) brain cancer studies; (3) recent*** **International Commission on Radiological Protection** ***(ICRP) and*** **United Nations Scientific Committee on the Effects of Atomic Radiation (*UNSCEAR) *reviews; and (4*) **National Council on Radiation Protection and Measurements** ***(NCRP) Report #159 on the risks of radiation-induced thyroid cancer.***

The calculations and results in the draft Blue Book are readily understood. ***The RAC recommends that EPA clarify the purpose and application of Blue Book contents by***

presenting in sufficient detail, in the first section, the contributions by the Blue Book to revising Federal Guidance Report (FGR) 13 and, in the last section, FGR 13 values of radionuclide risk coefficients. This information will enable the reader to evaluate the impact – if any – of Blue Book methodologies and values on changing FGR 13 values.

The RAC recommends that the EPA add to the accuracy, balance, and level of detail of the Blue Book by: (1) reporting risk estimates associated cohorts exposed to protracted low doses of ionizing radiation; (2) focusing on the major sources of error in uncertainty analysis; and (3) considering distinguishable types of cancer within a given organ.

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

Sincerely,

Dr. Deborah L. Swackhamer
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

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Science Advisory Board (SAB)
Radiation Advisory Committee (RAC)
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August 2009

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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 (U.S. EPA/ORIA 2008). In this draft "Blue Book", the EPA Office of Radiation and Indoor Air (ORIA) outlined proposed changes in the Agency's methodologies for estimating radiogenic cancer risks and gives examples of risk estimates for individual radiogenic cancers that it derived by the proposed methodologies. The EPA sought the RAC's advice on its draft Blue Book to assure reliable application for radiogenic cancer risk assessment in EPA programs, notably updating Federal Guidance Report (FGR) 13, *Health Risks from Low-level Environmental Exposure to Radionuclides* (U.S.EPA/ORIA 1999).

The RAC responded as follows to the itemized charge questions by ORIA:

Charge Question 1 on models not directly taken from BEIR VII

1a. The RAC agrees with the risk estimates proposed by the EPA for alpha particles that have greater linear energy transfer (LET) and relative biological effect (RBE) values than beta particles, gamma rays and x rays. For low-energy beta particles (notably tritium) and low-energy photons, on the other hand, the RAC finds that while the EPA review of information is sufficient to conclude that the RBE exceeds 1, it is insufficient for selecting appropriate RBE values. ***The RAC recommends that EPA staff encourage, for review by the scientific community, compilation and evaluationof information in a peer-reviewed journal and then selecty RBE values on this documentation and any follow-up discussion.***

1b. ***The RAC recommends – in contrast to BEIR VII -- use of a weighted arithmetic mean for each set of excess absolute risk (EAR) values 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 using either the arithmetic or the geometric mean, is that the arithmetic mean results from a linear addition and averaging of excess risk data, with equal emphasis on higher and lower values. The subsequent choice of weighting factor then explicitly captures judgments about the relative importance of the ERR- and EAR-based risk estimates. This approach has other benefits as well, such as consistency with uncertainty estimates. 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 advantage relative to the arithmetic mean.

1c. The RAC agrees with the approaches proposed by the EPA to derive risk estimates not specified in BEIR VII for solid cancers (kidney, skin) or for cancers associated with exposure to alpha-particle emitters (lung, liver). ***The RAC recommends that, for bone cancer, the EPA reconsider utilizing the radium data for the dial painter cohort (as asserted in the Blue Book, p.64, but not done), and, most importantly, apply recently published analyses of the data***. With regard to the liver, the RAC cautions that the organ is subject to tumors with diverse

histopathologies and possibly different outcomes. For leukemia, the RAC notes the uncertainty related to the EPA changing the RBE for alpha-particle radiation from 1 to 2 and suggests that the EPA reevaluate the data and logic on which this RBE increase is based before committing to the change.

1d. The RAC compliments the 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 (e.g., colon cancer) for which current survival rates are higher than previously.

1e. The RAC agrees with the EPA approach for separating from its overall risk estimates the risks for nonfatal skin cancer. Because of the high rate of spontaneous (nonradiogenic) nonmelanoma skin cancers and the experience that most nonmelanoma skin cancers respond to treatment, their inclusion with cancers that result in a much higher mortality rate would greatly distort the overall cancer morbidity and mortality risk estimate.

The RAC also agrees with use by the EPA for estimating the adult radiogenic cancer risk of the same model for exposure to radiation *in utero* or in childhood. Differences in risk estimates between the two groups were not statistically significant.

Charge Question 2 on uncertainty analysis

2a. The RAC considers the approach to uncertainty analysis in the draft Blue Book to be reasonable and comprehensive in deriving (1) overall risk estimate uncertainty from sampling variation, (2) the various model parameters, and (3) transfer of data to the U.S. population. ***The RAC recommends greater specificity, 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 summarize it in a table (in greater detail than is now in the Blue Book) with emphasis on the major sources of uncertainty and how each is quantified.

The RAC recommends that the Blue Book make the Bayesian uncertainty analysis as consistent as possible with the point estimates of risk. The EPA should justify use of two separate approaches to obtain best estimate values and confidence intervals.

The RAC recommends that EPA verify the uncertainty analysis by obtaining uncertainty intervals with a perturbation approach. The EPA should vary the value of each major contributor to uncertainty over a reasonable range to recalculate the corresponding range of the point estimate and demonstrate the validity of the recommended uncertainty.

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 can trace the basis of each decision concerning central value, uncertainty, and distribution, and have confidence in these characteristics.

Charge Question 3 on scientific defensibility, presentation, and completeness

3a. The RAC recognizes the scientific defensibility and appropriateness of the Blue Book**.** ***However, the RAC recommends that EPA enhance Blue Book contents by reporting further information from (1) studies of noncancer mortality; (2)brain cancer studies; (3) recent ICRP and UNSCEAR reviews; and (4) NCRP Report #159 on the risk of radiation-induced thyroid cancer*** (NCRP 2009).

3b. The RAC found that most of the calculations and results in the draft Blue Book are readily understandable. ***The RAC recommends that the EPA clarify the purpose and application of the Blue Book by presenting in detail, in the first section, the contributions by Blue Book contents in preparing Federal Guidance Report (FGR) 13 and, in the last section, FGR 13 values of radionuclide risk coefficients.*** This information should be sufficient to permit evaluating the impact of the Blue Book models and values on changing Federal radiation protection guides. The calculated values of radionuclide risk coefficients should be selected to show the reader whether significant changes in FGR 13 values are caused by this Blue Book or by the physiological models with which they will be combined.

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 that EPA expand its discussion of the following topics: (1) risk estimates associated with available studies of cohorts exposed to low-dose protracted radiation; (2) the major sources of error in the Bayesian uncertainty analysis; and (3) distinguishable types of cancer within a given organ.***

2. INTRODUCTION

2.1 Background

In 1994, the U.S. Environmental Protection Agency (EPA) published the report "*Estimating Radiogenic Cancer Risks*," (U.S. EPA 1994) often referred to as the "Blue Book", because of 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 *"The Effects on Populations Exposed to Low Levels of Ionizing Radiation BEIR III"* (NAS/NRC 1980) and the original Blue Book (U.S. 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 RBE. The 1994 EPA report replaced the 1984 EPA report.

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

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

In 2006, the National Research Council released *"Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2"*(NAS/NRC 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, the EPA prepared the draft "*White Paper: Modifying EPA Radiation Risk Models Based on BEIR VII"* (U.S. EPA/ORIA 2006) (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. The EPA 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 (U.S. EPA/SAB 2008) (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.

In December 2008, the ORIA issued the draft of the revised Blue Book, *"EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population"* (U.S. EPA/ORIA 2008), and asked the SAB to review it. The draft document contains specific methodology and its applications for estimating the risks of radiogenic cancer for many organs and tissues, with uncertainty estimates. It utilizes the advice contained in the BEIR VII, Phase 2 report, as well as in the SAB's advisory for the White Paper and the earlier Blue Book addendum, both described above. The Charge Memorandum (U.S. EPA/ORIA 2009) has the specific charge questions given in Section 2.3 below, provided to the SAB's augmented RAC with the completed draft document.

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). Additional public teleconferences took place on June 18, 2009 and July 22, 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 24, 2009, public teleconference (see 74 Fed. Reg., _____, August __, 2009; NOTE: Reserved for future Federal Register notice - - -KJK). 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, is impressively researched, scientifically sound and well written. Presentations by the EPA staff and 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/ORIA staff responded to all RAC requests and was forthcoming in explanations and clarifications.

2.3 EPA Charge to the Committee

2.3.1 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; U.S. EPA/ORIA 1999), 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 (NRC) of the National Academies of Sciences (NAS) 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* (NAS/NRC 2006) primarily addresses cancer and genetic risks from low doses of low-energy transfer (LET) radiation.

In a White Paper (U.S. EPA/ORIA 2006) 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 SAB review the attached draft document, *"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. The revised Blue Book will then serve as a basis for an updated version of FGR-13.

2.3.2 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) .[Note: the Sections indicated here refer to the draft EPA/ORIA Report.]
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 Sections 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 Section 1 cites the earlier Blue Book (U.S. EPA 1994) and the BEIR VII Report (NAS/NRC 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.

Section 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 radiation doses to exposures at low doses and low dose rates. A Dose/Dose Rate Effectiveness Factor (DDREF) is described for calculating the risk due to chronic low-dose and low-dose-rate radiation exposure. Several effects that have been observed or proposed at low doses are discussed, but are not invoked in subsequent calculations of risk. The authors present a survey of the epidemiologic evidence for radiogenic cancer risk, notably the 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 associated with 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 stationary year 2000 population mortality based on survival rates in the U.S. to obtain an estimate of the LAR per person-Gray (Gy) for the U.S. population

The process for obtaining LAR is described in Section 3. It is based on a set of parameter values for the ERR and EAR models in BEIR VII (Table 3-3). The EPA then uses a weighted geometric mean to combine the results from both the ERR and EAR models to obtain a point estimate of the excess risk, M (d,a,e), at an attained age a, following a single exposure to dose d, at age e. This value is applied to the stationary population to obtain the “best estimate” LAR. Section 3 also presents distinct approaches for breast cancer, leukemia, skin cancer, and residual cancer sites. Each of these cancer types is treated with a separate risk model.

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

Risk of radiogenic cancer associated with the high LET radiation of alpha particles is discussed in Section 5. Laboratory studies and human data are discussed. The latter include bone cancer associated with internal exposure to radium isotopes by injection (^{224}Ra) or ingestion (^{226}Ra, ^{228}Ra); liver cancer associated with administration of diagnostic doses of Thorotrast to patients, and plutonium intake by Russian 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.

Section 6 addresses risk from prenatal exposure to radiation. Induction of childhood cancer due to fetal radiation has been shown in various case-control studies (Stewart et al. 1958; MacMahon 1962; and other references in Section 6, p.96). While a causal link between *in utero* radiation exposure and childhood cancer is generally accepted (Doll and Wakeford 1997), some have termed the evidence for childhood cancers other than leukemia "equivocal" (Boice and Miller 1999).

The atomic bomb survivors provide the only data on radiation effects of adult-onset cancer risks among persons exposed *in utero* (Preston et al. 2008). The survivor data exhibit a statistically significant radiation dose response for adult-onset cancers with levels of risk that are considerably less than those reported for childhood cancers. There is also a weak suggestion that the radiation effect for those exposed *in utero* may be less than what has been seen for atomic bomb survivors exposed as children. The EPA decided to base risk estimates for childhood cancers following *in utero* exposure on the summary risk estimates presented in Doll and Wakeford (1997) and recommended by the International Commission on Radiological Protection (ICRP 2000), and risk estimates for adult-onset cancers on the corresponding risk estimates for childhood exposure.

In the very brief Section 7, application to calculating radionuclide risk coefficients is considered. The EPA will combine the revised excess cancer morbidity and mortality risk per person-Gy from this Blue Book with the latest available 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 FGR 13. The ORIA expects some increases and some decreases, depending on the radionuclide and 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, 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, the 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 the EPA proposes continuing use of models derived from BEIR VI (NAS/NRC 1994) to estimate the lung cancer risk from inhaled radon progeny; and

4) Bone cancer, for which the alpha-particle exposure risk per Gy is obtained from patients injected with ^{224}Ra. This value will be divided by and RBE of 10 to obtain the low-LET risk.

The RAC considers reasonable and generally acceptable the approach proposed by the EPA for obtaining cancer risk estimates for alpha particle emitters with the RBE values that the EPA proposes. Specific advice is given in response to question #1c (Section 3.4 below).

3.2.2 Low-Energy Electron and Photon Radiations

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

- Was this change recommended/suggested/implied in BEIR VII?
- Does ICRP, NCRP, UNSCEAR have similar recommendations?
- Does the NIOSH Interactive Radioepidemiological Program (IREP) use an RBE > 1?
- Is the scientific rationale for this change suitably mature at present (Hunter and Muirhead 2009)?
- What will be the reference source (1 MeV electrons and/or ^{60}Co)?
- Will this change be restricted only to radionuclides with energies similar to ^{3}H?
- How will "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 at specific energies, i.e., 1, 3 or 5 eV?
- Which radionuclides will be included and/or excluded?

In previous comments (U.S. EPA/SAB 2008) on the EPA White Paper (U.S. EPA/ORIA 2006), the RAC supported EPA use of an RBE of 2 – 2.5 for photons of energies less than 30 keV and for ^{3}H beta particles (18.6 to 0 keV). In light of this White Paper review and the current discussion, the RAC recommends that the EPA prepare detailed justification to support all proposed changes in the RBE values for low-LET ionizing radiations. The EPA should encourage preparation of a peer-reviewed publication that addresses these issues, consider the responses by the scientific community, and then revisit the proposed change in the RBE.

An important concern about the validity of the proposed change in the RBE (to ~ 1.4) for photon energies relates to diagnostic medical x rays. The draft Blue Book notes (on pages 72 and 95) that risk coefficients derived from studies of cohorts medically treated with x rays (at high but fractionated doses) in some cases differ from those observed for A-bomb survivors (Hunter and Muirhead 2009; Little 2001). Given that medical radiation exposures make up the majority of the average U.S. individual annual radiation dose (NCRP 2009a), the implications of a change in the RBE on the reported dose for individuals may be significant in the long term.

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 LAR estimates for the year 2000 US population. The EPA has proposed a method to comput0e an LAR 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. The EPA specifically asked the RAC about its decision to use an average excess rate function rather than averaging the ERR- and EAR-based LAR estimates. The 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 recommends that the LAR computation makes use of the weighted arithmetic mean instead of the choice described by the EPA. The RAC considers the arithmetic mean preferable even though this is a departure from the BEIR VII approach and even though the RAC endorsed the average rate method in its Advisory on the White Paper (U.S. EPA/SAB 2008). The primary reason for this current RAC recommendation is that the geometric mean implicitly tends toward the lower risk estimate whereas the arithmetic mean equally balances the low and high risk estimates. It is the selection of weights that explicitly captures judgments about the relative importance of the ERR- and EAR-based risk estimates for weighted arithmetic means. Furthermore, because the use of arithmetic means for risk estimates insures additivity of the age-specific risk estimates, the RAC 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 BEIR VII report does not discuss these issues; geometric means may have been used primarily because they simplified the analytical uncertainty assessment carried out for BEIR VII. Because the EPA uses 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 earlier) ICRP recommendations. The IREP also uses arithmetic means to combine relative-risk and excess-risk based estimates when computing probability of causation. Recent UNSCEAR reports (UNSCEAR 2000, 2008) present ERR- and EAR-based estimates, but do not combine them.

A key issue is the weighting of results by the two models. The general sense of the RAC is that weighting should emphasize ERR models more than EAR models except for outcomes with enough relevant data outside the LSS population (e.g., breast cancer) to indicate that EAR models transfer risk information more accurately. This emphasis appears in the point estimation process which, to the extent that it follows BEIR VII, places a weight of 0.7 on the ERR and 0.3 on the EAR results. Observations of tumor sites with different frequency of background occurrence, and sometimes also over different strains of experimental animals, show that ERR parameters tend to be more similar than EAR parameters (Storer et al. 1988). The RAC does recommend that the Blue Book include a brief discussion concerning the greater weight given to the ERR-based risks than to the EAR-based risks in most cases, but not all (for example, lung and breast cancer).

Use of arithmetic instead of geometric means for averaging results based on ERR and EAR models should improve consistency between the recommended point estimates and central estimates from the uncertainty analysis. To resolve remaining discrepancies, the RAC suggests that EPA make the prior distributions of weight parameters for the ERR and EAR models used in the uncertainty analysis more compatible with the provided point estimates.

One question that arises if weighted arithmetic means are used in place of weighted geometric means concerns the need to change the site-specific ERR/EAR weights recommended by BEIR VII. The RAC does not believe that the EPA should do so because BEIR VII members apparently were thinking in terms of linear (arithmetic) weights when they defined the weights used in their computations.

The RAC agrees with the EPA decision to use a stationary population rather than a census-based population in LAR computations. The reasons for this change were cogently described in the EPA staff presentation to the RAC. The RAC recommends that this discussion (including presentation of gender-specific population pyramids or age-adjusted rates for selected cancers) be included in the Blue Book to show the effect on solid cancer risk estimates of the switch from a census based population to a stationary population.

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 radiation, the proposed EPA kidney cancer risk calculation reasonably uses the BEIR VII residual cancers ERR model and the EAR model with an adjustment factor.

3.4.2 Bone

The RAC notes that its Advisory on the Agency Draft White Paper (U.S. EPA/SAB 2008) (Section 5.7, page 19) supported the use of 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 from these radionuclides. These approaches are outlined in the draft Blue Book (Section 4.2.2, page 64), but radium dial painter data apparently were not used. The more detailed approach considered 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 the biokinetics of ^{226}Ra and ^{228}Ra are different from those of ^{224}Ra.

When 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. 1997; Hoel and Carnes 2004).

3.4.3 Skin (Fatal and Nonfatal Nonmelanoma Cancers)

The EPA proposes, in draft Blue Book pages 31-32, to deviate from its previous approach (U.S. EPA 1994) based on ICRP recommendations (ICRP 1991) for estimating the risk of radiation-induced nonmelanoma skin cancer (NMSC). This change reflects 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 nonfatal (Shore 2001, 2002; Preston et al. 2007; Karagas et al. 1999; Ron et al. 1991), as stated in the draft Blue Book.

The RAC considers the proposed updated approach for deriving risk estimates for fatal and nonfatal NMSC to be reasonable and acceptable. This EPA approach applies its new model described in the Blue Book 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). The EPA also will use the revised DDREF value of 1.5 from BEIR VII to derive NMSC risk estimates in the low-dose range in place of the value 2 used previously.

3.4.4 Liver

The liver is recognized as a target organ for certain alpha-particle emitters. The relevance of the colloidal nature of 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, the EPA initially proposed the use of an RBE 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). The 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 the BEIR VII 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. However, because in the context of this report, ‘liver cancer’ (like ‘cancer’ in most other organs) is an all-embracing term that includes a diverse number of histopathologies, the RAC cautions that the uncertainties associated with grouping these different tumor histopathologies may outweigh any benefits gained by changing the RBE to 40.

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 (NAS/NRC 1994) 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 sufficient power to estimate risks. As noted in the draft Blue Book, 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; Sokolnikov et al. 2008) were consistent with an RBE of 20. The EPA proposes to use an RBE of 20 and the RAC considers this approach reasonable. The same value of 20 was recommended recently by the ICRP (2003, 2005).

Animal studies show RBE values at, above, and below 20. Some animal studies of radionuclides deposited in the lung obtained an RBE value of 20 or above (Gilbert et al. 1998; Hahn et al. 1999; Lundgren et al. 1995, 1996, 1997; Muggenburg et al. 1996, 2006) by comparing the effects of radionuclides that emit alpha particles with those that emit beta particles and gamma rays. Other animal studies suggest a much lower RBE (Priest et al. 2006). The RAC suggests caution in applying these values derived from animals that in many of these groups were exposed to doses above 1 Gy, well above the low-dose range. Results from such elevated doses have a strong influence on the shape of the dose response curve and the calculated RBE.

3.4.6 Leukemia

The draft Blue Book recommends an RBE of 2 for alpha-particle-induced leukemia based on human epidemiological studies at low doses of ^{224}Ra. This is a change from the value of 1 used in past EPA reports. The RAC considers that the RBE of 2 may be reasonable, but recommends that the Blue Book discuss the uncertainties in this value that derive from estimating doses from alpha-particle emitters and from different temporal patterns between the LSS and the ^{224}Ra group for the appearance of leukemia. Animal studies have not been helpful in understanding the RBE for alpha particles because of the variability in leukemia induction among strains (Storer et al. 1990); moreover, they have not had sufficient power to estimate leukemia risks from radiation (NAS-NRC 1990).

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. The 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 suggest that the modified method leads to more realistic breast cancer mortality risk estimates. The RAC believes that the EPA 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, with relatively high 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 the EPA proposal to update its approach by deriving risk estimates for incidence and mortality associated with radiation-induced NMSC from data for basal cell carcinoma (BCC) in the light of more recent epidemiological data. In particular, the RAC supports Shore's conclusion that essentially all NMSC induced by ionizing radiation in the low to moderate dose range are of the BCC type with a very low mortality rate (Shore 2001).

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

3.6.2 Prenatal Cancer Risk

The RAC considers that 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. The recent ICRP Report 103 (ICRP 2007) concluded that the DDREF value should remain at 2 and not be reduced to 1.5 as recommended by BEIR VII. The EPA should justify its decision to disagree with the ICRP conclusion and follow BEIR VII's recommendation.

In the draft Blue Book, the EPA accepts the absolute risk estimate of 0.06 Gy^{-1} of prenatal exposure for death from cancer prior to age 16 that was suggested by Doll and Wakeford (1997) and adopted by the ICRP (2000). Based on a review of the same studies considered by Doll and Wakeford, Boice and Miller (1999) expressed some skepticism about this estimate. However, the RAC considers it is reasonable to use the 0.06 Gy^{-1} risk estimate at this time. This evidence is largely derived from exposure to 80 kVp medical x rays; the risk coefficient should be adjusted to 0.04 Gy^{-1} if the EPA adopts an RBE of 1.4 for diagnostic medical x rays.

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 zero. 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 possible abortions were unaccounted for in the LSS, would lower the risk estimates, and should be mentioned by the EPA as an additional source of uncertainty for prenatal exposure effects.

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 has identified specific issues (described below) related to the uncertainty analysis which should be addressed to clarify assumptions and processes.

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 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 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. The Bayesian nature of the uncertainty analysis rests on 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 symmetric around the best estimate.

Beyond the mere fact that the EPA uncertainty analysis of LAR is Bayesian in nature, the Bayesian analysis for stomach and colon, for example, actually is a joint analysis of these cancers and combines information about the linear ERR parameters across these cancer types. It estimates a common mean (but separately by gender) 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 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 the other 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 latter parameters is in the LSS data.

4.2.2 Specific Comments

The 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, to replace the existing frequentist approach for the best estimate, accompanied by Bayesian methods to estimate the confidence interval.

Presumably, the 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 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, but 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 Monte Carlo Markov

Chain (MCMC) methodology can be demanding. For example, minor changes in starting values used in the simulations can have a large effect on the results. 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), 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 which parameters, either Type I or Type II, are the most influential in controlling the uncertainty intervals for LAR.

The RAC suggests that the 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 data 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 MCMC 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 process should indicate the operational range of the point estimate. In this way, one can verify whether the results of the current uncertainty analyses are appropriate for a given point estimate, and observe the width of the confidence interval 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. 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., Bolstad 2007).

When comparing the results of the draft Blue Book to previous estimates published in FGR 13, the EPA 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." The EPA should clarify how this information is 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 by directly assigning probability density functions to each parameter as shown in Table 4-1. Uncertainty of the Type II parameters is based on a different methodology. For these, a parameter is assumed to have a constant value (i.e., DDREF =1.5) and the uncertainty in the parameter is quantified by a multiplicative factor that is assigned a probability density such as LN (GM=1, GSD=1.35). The EPA should explain the reason for the two different approaches. 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 in Table 4-2 when LN (0.95, 1.1) is used for systematic errors in dosimetry or LN (1.1, 1.1) is used for uncertainty in selection bias.

4.2.3 Additional Comments on Risk Transfer

Risk due to radiation exposure may differ between populations for many reasons. Important issues such as population differences in genetic susceptibility to cancer and how such genetic differences would interact with radiation are only now beginning to be understood. Risk assessments by UNSCEAR, ICRP, BEIR VII and the draft Blue Book make the implicit assumption that, if the background rate of a particular cancer is similar in two populations, then the excess radiogenic cancer risk also will be similar. In reality, this assumption may be a simplification and as more about genes (or environmental exposures other than radiation) that interact with radiation is learned, other differences in gene or exposure frequency may be found between Japanese and U.S. 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 risk transfer models and the associated LAR calculations from the Japanese to U.S. populations.

For cancers with widely different baseline risks (e.g., stomach or prostate cancer) between the Japan and U.S. 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 U.S. data. One key Type II parameter is the weighting parameter that interpolates between the EAR and ERR models. The LSS data provide no direct information about whether EAR or ERR models are more reasonable because both models provide equivalent descriptions of the LSS data.

The uncertainty analysis gives only slight overall bias in favor of ERR compared to EAR models in the MCMC calculations. The tendency for the EAR models to be stressed more in the uncertainty analysis than in the point estimation may be the reason 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 to characterize uncertainty in parameters used in the models to obtain LAR, but recommends that the EPA clarify the reasoning for selecting the subjective priors used in the analysis (e.g., in Table 4-1). This information would also increase transparency in 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 models and assumptions for estimating risk presented in the draft Blue Book are broadly applicable and scientifically defensible. The EPA effort in the draft Blue Book to improve BEIR VII models and to apply other models for cancer risks that BEIR VII does not address is commendable. The draft Blue Book should be recognized as one in a chain of EPA publications that apply various models – especially those by BEIR VII for low-LET radiation – and lead to FGR 13 as a basis for radiation protection programs. The RAC suggests the following topics for additional consideration in preparing the Blue Book.

5.2.1 Noncancer Mortality

The draft Blue Book 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 (NAS-NRC 2006), 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). Because the identified radiation risks were small compared to baseline risks, age effects or the shape of the dose-response function could not be evaluated 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 non-cancer mortality in 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 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 be stated for not providing risk estimates for this endpoint at the present time.

5.2.2 Information from ICRP and UNSCEAR Reports

Since the publication of BEIR VII, both ICRP (2007) and UNSCEAR (2008) have published reports that include lifetime risk estimates for radiation-related cancers. The 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 the 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 draft Blue Book provides limited information regarding the risk of radiogenic thyroid cancer as estimated by BEIR VII, although the EPA discussed this issue extensively in its draft White Paper (U.S. EPA/ORIA 2006), where the EPA noted that "we now favor adoption of the NCRP thyroid cancer model, assuming that we would have a proper reference that can be cited."

This reference is now available in National Council on Radiation Protection and Measurements Report #159 (NCRP 2009). The RAC recommends that the EPA follow the NCRP approach, but also consider in its modeling the latest epidemiological data on exposures to the thyroid, published since the NCRP report was written in 2006. Particularly important are recent Chernobyl thyroid studies (Zablotska et al. 2008).

5.2.4 Radiogenic Brain Cancer

Information on an association between ionizing radiation and brain cancer has been generated from radiation-exposed cohorts that provide quantitative dose data and allow estimation of radiogenic risks. Based on data from multiple cohorts including A- bomb survivors, *tinea capitus*, hemangiomas, and childhood cancer survivors, the brain-tumor epidemiology literature has reached consensus that ionizing radiation is an established risk factor for brain tumor development (Ohgaki 2009, Bondy et al. 2008, Davis 2007). While brain tumors are complex histologically, radiation risk estimates for gliomas (the most common malignant brain tumor) are available from several of these cohorts. The RAC recommends that the EPA either include the radiogenic risk to the brain in the context of the other discussed cancer sites, or discuss the rationale for excluding the radiogenic risks to the brain in the Blue Book.

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; it suggests clarification of the following:

5.3.1 Tabular Presentations

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 eliminating repetition in several tables of the same values of lifetime risk estimates of cancer incidence or mortality.

5.3.2 Topical Organization and Content

The RAC recommends that at the beginning of the draft Blue Book, The EPA clearly state the intended purpose and application of the document, and anticipate 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, pages 29-32 (U.S. EPA/ORIA 2008), 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 by ORIA staff on March 23, 2009, clarified Blue Book contents and suggests that they be included in the Blue Book.

5.3.3 Relation of Input Information to Presented Results

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. Similarly, on page 55 is a statement that “the LAR for all cancers combined is increased by about 20%” because new SEER incidence data were used, followed by a statement that the models themselves would yield lower estimates of LAR than those published in FGR13 if the new models were applied to comparable mortality and incidence rates. The EPA appears to be making the 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.

The interplay between mathematic models and compiled incidence rates should be explained clearly and simply in the Blue Book to address concerns, heard from members of the

public who participated in the meetings, that the EPA will distort results to present inappropriately low risk values for implementation in the revised FGR 13. The rationale and implications of calculating LAR based on a life table for a hypothetical stable population rather than the existing life tables for the current US population also should be further explained to eliminate this approach as a cause of suspicion or distrust for the general reader.

5.3.4 Application of DDREF

The recent ICRP Report 103 (ICRP 2007) concluded that the DDREF value should remain at 2 and not be reduced to 1.5 as recommended by BEIR VII (U.S. NAS/NRC 2006). The EPA should justify their decision to disagree with the ICRP conclusion and follow BEIR VII's recommendation.

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 presents the scientific background material with appropriate accuracy, balance, and level of detail, but suggests that the following details be expanded upon:

5.4.1 Low-Dose Protracted Exposure

The RAC realizes that much of the draft Blue Book relies on BEIR VII risk estimates based primarily on LSS data, but better balance would be achieved by comparing and discussing differences in the revised EPA estimates and risk estimates from studies of persons exposed to low-level, protracted radiation exposure such as those of nuclear workers including the 15-country radiation worker study (Cardis et al. 2007) and the study of United Kingdom National Registry of Radiation Workers (Muirhead et al. 2009). The primary EPA concern is with the health effects of low-level, protracted radiation exposure, and acknowledges that risk estimates based on an acute exposure in a Japanese population are problematical when applied to low-level exposure of the U.S. population.

5.4.2 Cancer Sites with Limited Data

The RAC recommends that the EPA, in support for its rationale for estimating risk for specific cancer sites, look to the expected summary of cancer sites that have limited or inadequate data in the soon-to-be-published updated report by the International Agency for Research on Cancer (IARC) on the cancer risks of ionizing radiation. Specifically, justification should be given for estimating cancer risk for sites in which IARC concluded that the epidemiological data are inadequate or limited. Conversely, the EPA needs to justify having omitted any cancer sites for which IARC concluded that sufficient epidemiological evidence exists.

5.4.3 Cancer Subtypes

The RAC encourages expanding the discussion of issues related to lympho-hematopoietic cancers. For example, comment on: (1) recent discussions of whether chronic lymphocytic leukemia (CLL) is radiogenic (Linet et al. 2007; Schubauer-Berigan 2007a, 2007b; Vrijhead et al. 2008; Silver et al. 2007), and appropriate references contained within; (2) absence of risk estimates for leukemia subtypes; and (3) absence of risk estimates for non-Hodgkin's lymphoma or multiple myeloma.

5.4.4 Presentation of Stepwise EPA Development of Revised FGR 13

The RAC recommends that the EPA enhance its discussion in Section 7 of the Blue Book by including 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 is a model. Proposed values will enable both professionals and the public to evaluate the combined impact of revised cancer risk projections in the Blue Book and the selected recent dosimetric models and attributing the cause of revisions.

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APPENDIX A – EDITORIAL COMMENTS

Minor (editorial) comments on the draft EPA document on Radiogenic Cancer Risk.

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, 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 (it 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: Provide 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: The Gilbert et al. 2004 paper argued 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

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 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 Volt potential
LAR	Lifetime Attributable Risk
LET	Linear Energy Transfer
LN	Linear Non-Threshold (also LNT)
LSS	Life-Span Study
mGY	Milli (one Thousandth) Gray
M	Point estimate of the excess risk (d, a, e) [at an attained age, a, following a single exposure to a dose, d, at age, e]
MCMC	Markov Chain Monte Carlo methods
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
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
US	United States of America – used interchangeably with USA
WinBUGS	Windows (for Microsoft windows programs) for Bayesian inference Using Gibbs Sampling analysis software

End of Document