



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

--- Working Review Draft ---

EPA-SAB-RAC-ADV-07-xxx

The Honorable Stephen L. Johnson  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, DC 20460

Subject: Advisory on Agency Draft White Paper entitled “*Modifying Radiation Risk Models Based on BEIR VII,*”

Dear Administrator Johnson:

The Radiation Advisory Committee (RAC) of the Science Advisory Board has completed its review of the Agency’s draft white paper entitled “*Modifying EPA Radiation Risk Models Based on BEIR VII,*” dated August 1, 2006. In this white paper, the Agency’s Office of Radiation and Indoor Air (ORIA) outlined proposed changes in the EPA’s methodology for estimating radiogenic cancers. The EPA sought the RAC’s advice on the application of BEIR VII’s cancer risk estimates and on issues relating to the proposed modifications and expansions desirable or necessary for EPA’s purposes.

In providing advice to the Agency, the RAC had to consider the important distinction between the current state of scientific knowledge and the need for a practical, operational public health approach to radiation protection and standards setting. The RAC endorses EPA’s proposal to base its approach to low dose risk estimation on BEIR VII. Specifically, for purposes of establishing radiation protection policy, the RAC endorses the EPA’s use of a Linear Non-Threshold (LNT) model combined with the Dose and Dose Rate Effectiveness Factor (DDREF) for estimating risks following low dose exposures. By low dose, the RAC follows BEIR VII’s definition; that is, doses below 100 mSv (0.1Sv), in the context of low Linear Energy Transfer (LET) radiation. In endorsing the use of an LNT model for low dose risk estimation, the RAC wishes to emphasize that BEIR VII does not use a linear extrapolation of the risk derived from high doses to estimate the risk following low doses or low dose-rate exposures. The slope of the dose-response relationship at lower doses and dose rates is less than the slope in the high dose region. The ratio of slopes derived in the high and low dose regions is the DDREF. The RAC endorses the concept of using DDREF factors for estimating the risk in the low dose region.

1 The RAC agrees with the EPA that the BEIR VII methodologies using incidence models  
2 and data should be used wherever possible. The RAC accepts the EPA’s use of BEIR VII  
3 methodologies for deriving risk estimates for cancers of the stomach, colon, liver, prostate,  
4 uterus, ovary, bladder, and other solid tumors. The RAC did not find compelling evidence to  
5 suggest the use of the alternative lung cancer model discussed by EPA and recommends that the  
6 EPA use the BEIR VII methodologies for deriving risk estimates for radiogenic lung cancer risk.  
7 However, the RAC finds that the EPA is warranted in modifying the BEIR VII methodologies in  
8 several specific areas.

9  
10 The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A.  
11 population for a standard stationary population based on the year 2000 death rate, or fixed cohort  
12 is a reasonable adaptation of the BEIR VII approach. The RAC agrees that the EPA’s proposed  
13 use of the most current cancer-specific incidence and mortality rates available is an appropriate  
14 and scientifically valid adaptation of the BEIR VII approach.

15  
16 The RAC agrees with the EPA’s proposed approach for projecting risk estimates from the  
17 Japanese A-bomb survivors to the U.S.A. population by combining the age-specific results from  
18 the Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) models using the weighted  
19 geometric mean before calculating the lifetime attributable risk.

20  
21 The RAC concurs with EPA’s exploration of alternative methods for estimating the  
22 relative risk for radiogenic breast cancer. In particular, the RAC concurs with the EPA’s  
23 proposal to relate current breast cancer mortality rates to retrospective incidence rates rather than  
24 current incidence rates to better reflect the influence of life style changes, earlier breast cancer  
25 detection and treatment that could influence survival and hence mortality rates over an extended  
26 period.

27  
28 The RAC understands that EPA requires a rationale to estimate risks from exposures to  
29 higher LET radiation, especially alpha particles and lower energy photons and beta particles, but  
30 this subject was beyond the scope of BEIR VII. For alpha particles, the RAC is supportive of the  
31 use of a generally accepted Maximum Relative Biological Effectiveness ( $RBE_M$ ) value, such as  
32 20 which is currently being used. The RAC recommends using data specific to particular  
33 radionuclides where such human cancer risk data are available (e.g., lung, liver, bone, or bone  
34 marrow). For other organs and tissues, the RAC is supportive of the general approach of using  
35 the low-LET cancer risk from BEIR VII multiplied by  $RBE_M$ . The RAC concurs that an  
36 effectiveness factor in the range of 2 to 2.5 seems reasonable for low-energy photons and  
37 electrons for purposes of setting radiation protection standards.

38  
39 The RAC recognizes that although the BEIR VII committee chose not to provide risk  
40 estimates for non-melanoma skin cancer (NMSC) induced by ionizing radiation, EPA has an  
41 operational need for such estimates. The RAC supports EPA's proposed use of the 1991  
42 International Commission on Radiological Protection (ICRP) model to estimate the incidence  
43 and mortality risks of radiogenic NMSC. The RAC concurs with EPA that because of the high  
44 background incidence rates and low mortality due to NMSC, it is inappropriate to include risk  
45 estimates for radiogenic NMSC in the estimate of the total risk for radiogenic cancer.

1 The risk of bone cancer from low-LET radiation is not specified in the BEIR VII report  
2 but such information is required to consider the cancer risk from a bone-seeking beta-emitting  
3 radionuclide such as <sup>90</sup>Sr. The EPA proposes to divide the bone cancer risk observed in humans  
4 exposed to alpha particles from <sup>224</sup>Ra by an RBE to estimate the bone cancer risk from <sup>90</sup>Sr. The  
5 RAC concurs with this practical, operational approach to radiation protection.  
6

7 BEIR VII does not provide risk estimates for *in utero* exposure to radiation, but the EPA  
8 requires an estimate for its guidance documents. The RAC concludes that it would be reasonable  
9 for the EPA to base its risk estimates for *in utero* radiation exposure on those recommended by  
10 the ICRP for internally-deposited radionuclides.  
11

12 The RAC considers that it is premature for RAC to offer any advice to ORIA on thyroid  
13 cancer. A major review of radiogenic thyroid cancer is being completed by the National Council  
14 on Radiation Protection and Measurements (NCRP). This information should be considered by  
15 ORIA as it will reflect more recent or more relevant data that could improve the risk estimates  
16 provided by BEIR VII.  
17

18 The RAC strongly endorses the EPA-ORIA’s desire to estimate uncertainty bounds for its  
19 radiogenic cancer risk estimates. The uncertainty bound estimates should incorporate, to the  
20 extent possible, all sources of error and/or uncertainty, including the three main sources  
21 identified in BEIR VII (sampling variability in the Life Span Study (LSS) data, transport of risk  
22 from LSS to the U.S.A. population, and the appropriate value for DDREF at both high and low  
23 doses of low-LET radiation (or, equivalently, the appropriate use of the LNT dose-response  
24 model used for low dose extrapolation). Other sources of error and/or uncertainty identified by  
25 the EPA-ORIA (including dosimetry (of which neutron RBE is a factor), disease detection,  
26 disease classification, temporal patterns, and appropriate RBE values) should also be considered.  
27

28 The RAC considered several additional complications that could influence uncertainty.  
29 The significant biological responses from the LSS and other epidemiological data cover a limited  
30 range of individual doses. The uncertainties associated with risk estimates are smallest for doses  
31 where cancer rates are significantly elevated. At doses below this range, risk estimates are based  
32 on an assumed LNT dose-response model and method of extrapolation from higher-dose/higher-  
33 response data. In such a situation, lower-dose risk estimates may have larger relative  
34 uncertainties than higher-dose risk estimates because of this extrapolation. In BEIR VII and the  
35 EPA-ORIA’s proposed approach to uncertainty estimation, this “additional” uncertainty is  
36 contained within the uncertainty in the value for DDREF, since DDREF is only invoked at lower  
37 doses. The RAC thus strongly endorses the EPA-ORIA’s intention to include uncertainty in  
38 DDREF in the overall uncertainty analysis.  
39

40 BEIR VII specifically considered adaptive response, genomic instability, and bystander  
41 effects, and concluded that currently there is insufficient evidence to explicitly add these effects  
42 to the dose-response model. In the absence of compelling scientific evidence to do otherwise,  
43 the RAC endorses the EPA-ORIA’s plan to follow BEIR VII and use the LNT for calculation of  
44 radiation risk. The RAC does recommend, however, that the EPA-ORIA include a (qualitative)  
45 discussion of modern cellular and molecular biological concepts in its final report. As a  
46 cautionary note, the RAC recommends that the EPA discuss potential problems associated with



**NOTICE**

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This advisory has been written as part of the activities of the 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 advisory has not been reviewed for approval by the Agency and, hence, the contents of this advisory 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>.

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**U.S. Environmental Protection Agency  
Science Advisory Board**

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--- (Roster to be Inserted in Later Drafts) ---

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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 white paper entitled “*Modifying EPA Radiation Risk Models Based on BEIR VII*,” dated August 1, 2006 (U.S. EPA. ORIA. 2006a). In this white paper, the Agency’s Office of Radiation and Indoor Air (ORIA) outlined proposed changes in the EPA’s methodology for estimating radiogenic cancers. The EPA sought the RAC’s advice on the application of BEIR VII’s (U.S. NAS/NRC 2006) cancer risk estimates and on issues relating to proposed modifications and expansions desirable or necessary for EPA’s purposes.

In providing advice to the Agency, the RAC had to consider the important distinction between the current state of scientific knowledge and the need for a practical, operational public health approach to radiation protection and standards setting. The RAC endorses EPA’s proposal to base its approach to low dose risk estimation on BEIR VII. Specifically, for the purposes of establishing radiation protection policy, the RAC endorses the EPA’s use of a Linear Non-Threshold (LNT) model combined with the Dose and Dose Rate Effectiveness Factor (DDREF) for estimating risks following low dose exposures. By low dose, the RAC follows BEIR VII’s definition; that is, doses below 100 mSv (0.1Sv), in the context of low Linear Energy Transfer (LET) radiation. In endorsing the use of an LNT model for low dose risk estimation, the RAC wishes to emphasize that BEIR VII does not use a linear extrapolation of the risk derived from high doses to estimate the risk following low dose or low dose-rate exposures. The slope of the dose response relationship at lower doses and dose rates is less than the slope in the high dose region. The ratio of slopes derived in the high and low dose regions is the DDREF. The RAC endorses the concept of using DDREF factors for estimating the risk in the low dose region.

With respect to recent advances in the scientific knowledge of radiation biology and carcinogenesis, the RAC wishes to emphasize that considerable uncertainties remain in the risk estimates for radiation-induced cancers, especially at low doses and low dose rates. The epidemiological data below 100 mSv are not sufficient by themselves for risk estimation and considerable cellular and animal data suggest complexities beyond the application of a simplified deoxyribonucleic acid (DNA) damage model which historically has been used as support for an LNT dose-response model. The RAC also emphasizes the additional complexities introduced with varying RBE and dose-rate. Thus, while the RAC endorses EPA’s use of the LNT model, the Agency is advised to continue to monitor the scientific basis of the relationship between low dose effects and cancer risk.

The RAC agrees with the EPA that the BEIR VII methodologies using incidence models and data should be used wherever possible. The RAC accepts the EPA’s use of BEIR VII methodologies for deriving risk estimates for cancers of the stomach, colon, liver, prostate, uterus, ovary, bladder, and other solid tumors. The RAC did not find compelling evidence to suggest the use of the alternative lung cancer model discussed by EPA and recommends that the EPA use the BEIR VII methodologies for deriving risk estimates for radiogenic lung cancer risk. However, the RAC finds that the EPA is warranted in modifying the BEIR VII methodologies in several specific areas as discussed below.

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The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A. population for a standard stationary population based on the year 2000 death rate, or fixed cohort is a reasonable adaptation of the BEIR VII approach. It is consistent with the EPA’s established approach to cancer risk estimation from exposures to chemicals.

The RAC agrees that the EPA’s proposed use of the most current cancer-specific incidence and mortality rates available is an appropriate and scientifically valid adaptation of the BEIR VII approach.

The RAC agrees with the EPA’s proposed approach for projecting risk estimates from the Japanese A-bomb survivors to the U.S.A. population by combining the age-specific results from the Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) models using the weighted geometric mean before calculating the lifetime attributable risk. This approach is a modification of that used in BEIR VII, but it has the advantage of allowing the risk results from multiple exposures to be integrated, enabling the risk from chronic lifetime exposure to be calculated. Additionally, this method was previously used by the EPA in FGR 13.

The RAC concurs with EPA’s exploration of alternative methods for estimating the relative risk for radiogenic breast cancer. In particular, the RAC concurs with the EPA’s proposal to relate current breast cancer mortality rates to retrospective incidence rates rather than current incidence rates to better reflect the influence of life style changes, earlier breast cancer detection and treatment that could influence survival and hence mortality rates over an extended period.

The RAC understands that EPA requires a rationale to estimate risks from exposures to higher LET radiation, especially alpha particles and lower energy photons and beta particles, but this subject was beyond the scope of BEIR VII. For alpha particles, the RAC is supportive of the use of a generally accepted Maximum Relative Biological Effectiveness ( $RBE_M$ ) value, such as 20 which is currently being used. For those radionuclides for which human cancer risk data are available (lung, liver, bone, or bone marrow), the RAC recommends that this information be used directly whenever possible. For other organs and tissues, the RAC is supportive of the general approach of using the low-LET cancer risk from BEIR VII multiplied by  $RBE_M$ .

For low-energy photons and electrons, the EPA white paper suggests that the Relative Biological Effectiveness (RBE) for medical x-rays is about 2 to 2.5. X-rays are not uniquely different from gamma rays, so the RAC recommends that any risk estimate association with exposure to photons should be correlated with energy rather than the method of production. The RAC concurs that an effectiveness factor in the range of 2 to 2.5 seems reasonable for low-energy photons and electrons for purposes of setting radiation protection standards.

The RAC recognizes that although the BEIR VII committee chose not to provide risk estimates for non-melanoma skin cancer (NMSC) induced by ionizing radiation, EPA has an operational need for such estimates. The RAC supports EPA's proposed use of the 1991 International Commission on Radiological Protection (ICRP) model to estimate the incidence and mortality risks of radiogenic NMSC taking into account more recent findings that most of

1 the NMSCs attributable to low to moderate doses of LET ionizing radiation are of the basal cell  
2 carcinoma (BCC) type (Shore .2001.), and that the incidence rates of BCC have been increasing  
3 substantially in recent decades among the general population (Karagas et al. .1999.). However,  
4 the RAC concurs with EPA that because of the high background incidence rates and low  
5 mortality due to NMSC, it is inappropriate to include risk estimates for radiogenic NMSC in the  
6 estimate of the total risk for radiogenic cancer.

7  
8 The risk of bone cancer from low-LET radiation is not specified in the BEIR VII report  
9 but such information is required to consider the cancer risk from a bone-seeking beta-emitting  
10 radionuclide such as <sup>90</sup>Sr. The EPA proposes to divide the bone cancer risk observed in humans  
11 exposed to alpha particles from <sup>224</sup>Ra by an RBE to estimate the bone cancer risk from <sup>90</sup>Sr. The  
12 RAC concurs with this practical, operational approach to radiation protection.

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14 BEIR VII does not provide risk estimates for *in utero* exposure to radiation, but the EPA requires  
15 an estimate for its guidance documents. The RAC concludes that it would be reasonable for the  
16 EPA to base its risk estimates for *in utero* radiation exposure on those recommended by the  
17 ICRP for internally-deposited radionuclides.

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19 The RAC considers that it is premature for RAC to offer any advice to ORIA on thyroid  
20 cancer. A major review of radiogenic thyroid cancer is being completed by the National Council  
21 on Radiation Protection and Measurements (NCRP). This information should be considered by  
22 ORIA as it will reflect more recent or more relevant data that could improve the risk estimates  
23 provided by BEIR VII.

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25 The RAC strongly endorses the EPA-ORIA’s desire to estimate uncertainty bounds for its  
26 radiogenic cancer risk estimates. The uncertainty bound estimates should incorporate, to the  
27 extent possible, all sources of error and/or uncertainty, including the three main sources  
28 identified in BEIR VII (sampling variability in the Life Span Study (LSS) data, transport of risk  
29 from LSS to the U.S.A. population, and the appropriate value for DDREF at both high and low  
30 doses of low-LET radiation (or, equivalently, the appropriate use of the LNT dose-response  
31 model used for low dose extrapolation). Other sources of error and/or uncertainty identified by  
32 the EPA-ORIA (including dosimetry of which neutron RBE is a factor), disease detection,  
33 disease classification, temporal patterns, and appropriate RBE values) should also be considered.

34  
35 The RAC considered several additional complications that could influence uncertainty.  
36 To begin with, the significant biological responses from the LSS and other epidemiological data  
37 cover a limited range of individual doses. The uncertainties associated with risk estimates are  
38 smallest for doses where cancer rates currently are statistically significantly different from the  
39 spontaneous cancer rates. At doses below this range, risk estimates are based on an assumed  
40 LNT dose-response model and method of extrapolation from higher-dose/higher-response data.  
41 In such a situation, lower-dose risk estimates may have larger relative uncertainties than higher-  
42 dose risk estimates because of this extrapolation.

43  
44 BEIR VII specifically considered adaptive response, genomic instability, and bystander  
45 effects, and concluded that currently there is insufficient evidence to explicitly add these effects  
46 to the dose-response model. The EPA-ORIA proposes at the present time to follow BEIR VII

1 and use the LNT combined with a DDREF for calculation of radiation risk. In the absence of  
2 compelling scientific evidence to do otherwise, the RAC endorses the EPA-ORIA’s plan in this  
3 regard. The RAC does recommend, however, that the EPA-ORIA include a (qualitative)  
4 discussion of modern cellular and molecular biological concepts in its final report. As a  
5 cautionary note, we recommend that the EPA discuss potential problems associated with the use  
6 of LNT risk estimates in very low dose settings where cancer rates currently are not statistically  
7 significantly different from spontaneous cancer rates and where the doses are a fraction of those  
8 associated with exposure to background radiation.  
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10 It is important to note that there is indeed opportunity to include uncertainties in the  
11 model – that is, uncertainties in high-dose versus low dose behavior – in the overall uncertainty  
12 analysis. In BEIR VII and the EPA-ORIA’s proposed approach to uncertainty estimation, this  
13 “additional” uncertainty is contained within the uncertainty in the value for DDREF, since  
14 DDREF is only invoked at lower doses. The RAC thus strongly endorses the EPA-ORIA’s  
15 intention to include uncertainty in DDREF in the overall uncertainty analysis.  
16

17 Uncertainties in risk estimates also change as a function of time into the future, being  
18 smallest in the near time frame. This is due to several factors, including changes in future  
19 (actual) populations (as opposed to a ‘stationary population’), future background cancer  
20 incidence, and future medical advances (since the case fatality rate may decrease as a result of  
21 better treatment interventions in the future). Uncertainties thus become greater as the risk  
22 estimates are applied further into the future. The RAC recommends that EPA-ORIA include a  
23 (qualitative) discussion of these concepts in its final report.  
24

25 An additional source of uncertainty in risk estimates is associated with the mechanistic  
26 biophysical model that is used in BEIR VII to support the LNT in the low dose region. In  
27 Appendix A, the RAC provides a brief review of current research and recommends that ORIA  
28 remain aware of the research continuously updating the biophysical model used to support the  
29 estimates of radiation risk following low dose radiation exposure.  
30

31 These recent advances provide a scientific basis for the observed non-linear dose-  
32 response relationships seen in many biological systems (BEIR VII, Ko et al. 2006, Mitchel et al.  
33 2004). They suggest that the mechanism of action of radiation-induced damage is different  
34 following exposure to high doses than it is after low radiation doses. It becomes important to  
35 consider new paradigms associated with the biological responses to low doses of radiation and to  
36 modify and further develop the models used to support the extrapolation of dose-response  
37 relationships into dose regions where it is not possible to measure changes in radiation-induced  
38 cancer incidence/mortality in human populations.  
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## 2. INTRODUCTION

### 2.1 Background

In 1994, the EPA published a report, referred to as the “Blue Book,” which lays out the EPA’s methodology for quantitatively estimating radiogenic cancer risks (U.S. EPA. 1994) <http://epa.gov/radiation/docs/assessment/402-r-93-076.pdf>. A follow-on report made minor adjustments to the previous estimates and presented a partial analysis of the uncertainties in the numerical estimates (U.S. EPA. 1999a) <http://epa.gov/radiation/docs/assessment/402-r-99-003.pdf>. Finally, the Agency published Federal Guidance Report 13 (U.S. EPA. 1999) <http://epa.gov/radiation/docs/federal/402-r-99-001.pdf> which utilized the previously published cancer risk models, in conjunction with International Commission on Radiological Protection (ICRP) dosimetric models and the U.S.A. usage patterns, to obtain cancer risk estimates for over 800 radionuclides, and for several exposure pathways. These were later updated (U.S. EPA. 1999b) <http://epa.gov/radiation/federal/techdocs.htm#report13>.

The National Research Council (NAS/NRC) recently released *Health Risks from Exposure to Low levels of Ionizing Radiation BEIR VII Phase 2* which primarily addresses cancer and genetic risks from low doses of low-LET radiation (BEIR VII) (U.S. NAS/NRC. 2006) <http://newton.nap.edu/catalog/11340.html#toc>). In the EPA draft *White Paper: Modifying EPA Radiation Risk Models Based on BEIR VII*, the Agency proposes changes to the EPA’s methodology for estimating radiogenic cancers, based on the contents of BEIR VII (U.S. EPA. 2006a). The Agency expects to adopt the models and methodology recommended in BEIR VII, but believes that certain modifications and expansions are desirable or necessary for the EPA’s purposes.

#### 2.1.1 Request for EPA Science Advisory Board (SAB) Review

The Radiation Advisory Committee (RAC) was initially briefed on the draft White Paper topic at its public planning meeting of December 21, 2005 which was held at the National Air and Environmental Radiation Laboratory (NAERL) in Montgomery, Alabama (see 70 Fed. Reg. 69550, November 16, 2005). ORIA issued its external draft White Paper entitled “*Modifying EPA Radiation Risk Models Based on BEIR VII*,” on August 1, 2006 (U.S. EPA. 2006a). The charge questions to the SAB were formally submitted on August 31, 2006 (U.S. EPA. 2006b).

The SAB RAC met in a public teleconference meeting on September 6, 2006 and conducted a face-to-face public meeting on September 26, 27 and 28, 2006 for this advisory (see 71 Fed. Reg. 45545, August 9, 2006). Additional public conference calls took place on November 28, 2006, December 18, 2006, and March 9, 2007 (see 71 Fed. Reg., 62590, October 26, 2006 and add additional meetings as appropriate - - - KJK). 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>).

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## **2.2 Proposed EPA Adjustments and Extensions to BEIR VII Models**

### **2.2.1 Current EPA Cancer Risk Models**

For most cancer sites, radiation risk models are derived primarily from epidemiologic data from the Life Span Study (LSS) of the atomic bomb survivors. The EPA’s models for esophageal, stomach, colon, lung, ovarian, bladder and “residual” cancers and leukemia were adapted from the models published by Land and Sinclair based on a fit to the linear non-threshold (LNT) fit to the LSS data (Land and Sinclair. 1991.).

For each solid tumor site, gender, and age-at-exposure interval, there is a model providing a coefficient for the excess relative risk (ERR) per gray (Gy) for cancer mortality, which is assumed to be constant beginning at the end of a minimum latency period until the end of life. Land and Sinclair present two sets of models known as the “multiplicative” and the “National Institutes of Health (NIH)” models that differ in how one “transports” risk from the Japanese LSS population to the United States population. In the multiplicative model, it is assumed that the ERR/Gy is the same in all populations, whereas, in the NIH model, it is assumed that the excess absolute risk (EAR) is the same in different populations for the limited period of epidemiological follow-up. Given the scarcity of information on how radiogenic cancer risk varies between populations having differing baseline cancer rates, the EPA previously adopted an intermediate geometric mean coefficient “GMC” model for each site, where the risk coefficients were taken to be the weighted geometric mean of the corresponding ERR and EAR coefficients for both the multiplicative and the NIH models (U.S. EPA. 1994).

For leukemia, the treatment of the temporal response in the models was more complex, but the approach for transporting risk to the U.S.A. population was analogous. Following the approach of Land and Sinclair, the EPA also developed a GMC model for kidney cancer from the LSS data. The EPA’s models for other site- or type-specific cancers, including breast, liver, thyroid, bone, and skin were based on various authoritative reports (NCRP. 1980.; NRC. 1988.; ICRP. 1991a, b; Gilbert. 1991.). Based primarily on ICRP recommendations at that time (ICRP 1991a), for low doses and dose rates, each coefficient was reduced by a factor of two, dose and dose-rate effectiveness factor (DDREF), from that which would be obtained from a LNT fit to the LSS data.

### **2.2.2 BEIR VII Models**

BEIR VII cancer site-specific models derived from the LSS differ from those of Land and Sinclair in several notable ways: (1) they are derived primarily from cancer incidence rather than cancer mortality data; (2) mathematical fitting is performed to better reflect the functional dependence of solid cancer risk on age at exposure and attained age, (i.e., age at diagnosis of a cancer or age at death due to cancer depending on the end-point of interest); (3) a weighted average of risk projection models is used to transport risk from the LSS to the U.S.A. population;

1 (4) a value for the DDREF of 1.5 is estimated from the LSS and laboratory data; (5) quantitative  
2 uncertainty bounds are provided for the site-specific risk estimates in BEIR VII.

3  
4 For breast cancer and thyroid cancer, BEIR VII risk models are based on pooled analyses  
5 of data from the LSS cohort, together with data from epidemiologic studies of medically  
6 irradiated cohorts (Preston et al. 2002; Ron et al. 1995).

### 7 8 **2.2.3 Proposed EPA adjustments and Extensions to BEIR VII Models**

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10 In the draft *White Paper: Modifying EPA Radiation Risk Models Based on BEIR VII*  
11 (U.S. EPA. ORIA .2006a.), the Agency’s Office of Radiation and Indoor Air (ORIA) outlined  
12 proposed changes in the EPA’s methodology for estimating radiogenic cancers, based on the  
13 contents of BEIR VII and some ancillary information. For the most part, the Agency expects to  
14 adopt the models and methodology recommended in BEIR VII; however, the Agency believes  
15 that certain modifications and expansions are desirable or necessary for the EPA’s purposes.  
16 The objective of BEIR VII was to derive/update cancer risk estimates for radiation exposures of  
17 100 mSv or less, primarily from external photon radiation based on the most current valid  
18 epidemiological and experimental data available. In order to satisfy EPA’s broader mission, the  
19 EPA needs to have a basis for estimation of cancer risks outside BEIR VII’s scope.

20  
21 One significant extension to be considered is the estimation of cancer risks from  
22 exposures to higher Linear Energy Transfer (LET) radiations, especially to alpha particles, and  
23 also to lower energy photons and beta particles. An important expansion proposed by EPA to be  
24 considered is the estimation of risks from exposures to alpha particles, and also to alpha emitters  
25 deposited in the lung and the bone. BEIR VII does not present any risk estimates for radiogenic  
26 bone cancer. The EPA proposes to estimate bone cancer risk from data on radium injected  
27 patients and to multiply that risk by a quality factor to estimate the risk from internally deposited  
28 beta-gamma emitting radioactive materials.

29  
30 BEIR VII does not provide quantitative estimates of risk for skin cancer. It does not fully  
31 address prenatal exposures. BEIR VII presents a model for estimating the risk of the radiogenic  
32 thyroid cancer incidence, but not of mortality due to radiogenic thyroid cancer.

33  
34 The EPA proposes to use somewhat different population statistics from BEIR VII.  
35 Consideration is given to an alternative model for estimating radiogenic lung cancer. For breast  
36 cancer, the EPA proposes an alternative method for estimating mortality, which takes into  
37 account changes in incidence rates and survival rates over time.

38  
39 At this point in its activity on this topic, the EPA is seeking advice from the Agency’s  
40 Science Advisory Board’s (SAB) Radiation Advisory Committee (RAC) on the application of  
41 BEIR VII’s cancer risk estimates and on issues relating to these modifications and expansions.  
42 After receiving the advisory review, the Agency plans to implement changes in their  
43 methodology through the publication of a revised Blue Book, which it would expect to submit to  
44 the SAB’s RAC or a specialty panel supplementing the RAC for final review. The revised Blue  
45 Book could then serve as a basis for an updated version of FGR-13.

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1           **2.2.4    Uncertainty Estimates**  
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3           BEIR VII provides quantitative uncertainty bounds for each of its risk coefficients,  
4 however, no uncertainty was assigned to the form of the dose-response relationship. It was  
5 implicitly assumed that the dose-response relationship followed the hypothetical dose-response  
6 curve depicted in Figure 10-1. This shows a progression of linear approximations, with different  
7 slopes within different dose ranges. The relationship between these different slopes provides the  
8 definition of the DDREF. This progression allowed the BEIR VII Committee to place  
9 uncertainty on bounds of the DDREF. Mechanisms pertaining to the biological effects of low-  
10 level ionizing radiation are being investigated. This could eventually mandate a different dose-  
11 response model, potentially resulting in changes in estimates of risk at low doses. Assigning  
12 probabilities to alternative models would be highly subjective at this time. The EPA does not  
13 propose to quantify the uncertainty pertaining to low-dose extrapolation, but it would provide a  
14 brief discussion of the issue.  
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16           **2.2.5    Level of Review**  
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18           There are various levels of reviews which EPA can request from the SAB. These include  
19 reviews, advisories, and commentaries. The request from EPA-ORIA was for an “advisory”  
20 review of the draft White Paper. ORIA was interested in vetting ideas with a group of scientific  
21 experts on how to incorporate the changes in cancer risk models described by BEIR VII and to  
22 extend the BEIR VII models to areas not specifically addressed by the BEIR VII committee.  
23 ORIA described it as a “mid-course correction” which would allow the RAC to provide advice  
24 on a series of questions which would guide the Agency in incorporating the latest scientific  
25 thinking into their risk estimates. The RAC was not asked to provide policy direction,  
26 therefore the RAC did not consider the implications to EPA standards which may be an outcome  
27 of the changes to the risk estimates.  
28

29           **2.2.6    Specific Charge to the Committee**  
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- 31
- 32    1)       *BEIR VII provides incidence models for many cancer sites as a basis for calculating the*  
33 *risk from low-dose, low-LET radiation. Please comment on EPA’s application of this overall*  
34 *approach as described in the draft White Paper.*  
35
- 36    2)       *In addition to the overall approach described in BEIR VII, the draft White Paper presents*  
37 *specific modifications and extensions. Please comment on the soundness of the following*  
38 *proposals:*  
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- 40       a.       *Calculation of the risk to the life table (stationary) population instead of the actual*  
41 *U.S. population (see Sections II.A.-C.); this is consistent with our current approach.*  
42
- 43       b.       *Use of more recent incidence and mortality data from SEER and/or other sources*  
44 *(see Section II.D.); BEIR VII used a previous version of SEER data for the years*  
45 *1995-1999.*  
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- 1 c. *Method for combining BEIR VII’s models for projecting risk from Japanese A-bomb*  
2 *survivors to U.S. population (see Section II.E.). In contrast to BEIR VII, we propose*  
3 *to combine the two risk models before integration to calculate the lifetime*  
4 *attributable risk.*  
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6 d. *Adoption of an alternative model for radiogenic lung cancer risk which may better*  
7 *account for the effects of smoking than the BEIR VII approach (see Section II.G.).*  
8  
9 e. *Method for calculating breast cancer mortality risk, accounting for the relatively long*  
10 *time from detection until death (see Section II.H.).*  
11  
12 f. *Proposed approaches for extending risk estimates to radiations of different LET’s - in*  
13 *particular, deriving site-specific risk estimates for alpha or x radiations based on*  
14 *models derived from the A-bomb survivors, who were primarily exposed to gamma*  
15 *rays (see Section III).*  
16  
17 g. *Estimation of risks for sites not specified in BEIR VII, specifically bone and skin, for*  
18 *which we propose to update our current approaches (see Sections III.A. and V,*  
19 *respectively).*  
20  
21 h. *Estimation of risk due to prenatal exposure. EPA’s current lifetime risk estimates do*  
22 *not include risk from prenatal exposure, and BEIR VII does not provide them. The*  
23 *draft White Paper uses ICRP recommendations to project its risks of childhood*  
24 *cancers induced by in utero exposure. Please comment on the soundness of the*  
25 *approach described in the draft White Paper to apply ICRP as described in Section*  
26 *IV.*  
27  
28 3) *BEIR VII provides quantitative uncertainty bounds for each of its risk coefficients. EPA*  
29 *proposes to adopt this methodology with some additional discussion of the uncertainties not*  
30 *quantified in BEIR VII. Please comment on the adequacy of this approach (see Section II.K.).*  
31  
32 4) *In Section VI, the draft White Paper discusses some issues relating to radiogenic thyroid*  
33 *cancer. Does the RAC have any specific suggestions for dealing with this risk; e.g., does the*  
34 *RAC have any advice on gender specificity, effectiveness of iodine -131 compared to gamma*  
35 *rays, or estimation of thyroid cancer mortality?*

1                                   **3. PHILOSOPHY OF APPROACH TO THE CHARGE**

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3                   **3.1     Responding to the Agency’s Specific Request**

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5                   In providing advice to the Agency, the RAC had to consider the important distinction  
6 between the current state of scientific knowledge and the need for a practical, operational public  
7 health approach to radiation protection and standards setting. In this Advisory, the RAC wishes  
8 to comment on both issues.

9  
10                  For the purposes of providing estimates of the risks of radiation-induced cancers as a  
11 basis for setting radiation protection standards, the RAC endorses EPA's proposal to base its  
12 approach to low dose risk estimation on BEIR VII. Specifically, for purposes of establishing  
13 radiation protection policy, the RAC endorses the use of an LNT model combined with the  
14 DDREF for estimating risks following low dose exposures.. By “low dose,” the RAC follows  
15 BEIR VII’s definition; that is, doses below 100 mSv (0.1 Sv), in the context of low-LET  
16 radiation. In endorsing the use of an LNT model for low dose risk estimation, the RAC wishes  
17 to emphasize that BEIR VII does not use a linear extrapolation of the risk derived from high  
18 doses to estimate the risk following low doses or low dose-rate exposures. The slope of the  
19 dose-response relationship at lower doses and dose rates is less than the slope in the high dose  
20 region. The ratio of slopes derived in the high and low dose regions is the DDREF. The RAC  
21 endorses the concept of using DDREF factors for estimating the risk in the low dose region  
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23                  With respect to recent advances in the scientific knowledge of radiation biology and  
24 carcinogenesis, the RAC wishes to emphasize that considerable uncertainties remain in the risk  
25 estimates for radiation-induced cancers, especially at low doses and low dose rates. As BEIR  
26 VII acknowledges, the epidemiological data below 100 mSv (0.1 Sv) are not sufficient by  
27 themselves for risk estimation, and considerable cellular and animal data suggest complexities  
28 beyond the application of a simplified DNA damage model which historically has been used as  
29 support for an LNT dose-response model. The RAC also wishes to emphasize the additional  
30 complexities introduced with varying RBE and dose rate. Thus, while the RAC endorses EPA’s  
31 use of the LNT model, the Agency is advised to continue to monitor the science relating to low  
32 dose effects and cancer induction.  
33

34                  Additional discussion of the biophysical models of radiation effects in the low dose  
35 region is in Appendix A.

36                   **3.2     Acknowledgement**

37  
38                  The document “*Modifying EPA Radiation Risk Models Based on BEIR VII,*” August 1,  
39 2006 was well written and provided much needed background. Similarly, with the BEIR VII  
40 report, presentations by the ORIA staff and other information provided to the RAC in the course  
41 of the public meetings were found to be helpful. During the meetings, the ORIA staff worked  
42 diligently to augment their draft *White Paper* with additional pieces of information that the RAC  
43 felt were necessary to assist with the advisory. The staff took care to honor all the RAC’s

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1 requests and demonstrated their patience as members sought to understand all that went into the  
2 modified procedures being proposed.  
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## **4. RESPONSE TO CHARGE QUESTION 1: APPLICATION OF THE OVERALL APPROACH AS DESCRIBED IN THE DRAFT WHITE PAPER**

### **4.1 Response to Charge Question 1:**

*BEIR VII provides incidence models for many cancer sites as a basis for calculating the risk from low-dose, low-LET radiation. Please comment on EPA’s application of this overall approach as described in the draft White Paper.*

The Radiation Advisory Committee (RAC) agrees with the EPA that the BEIR VII methodologies using incidence models and data should be used wherever possible. The RAC accepts the EPA’s use of BEIR VII methodologies for deriving risk estimates for cancers of the stomach, colon, liver, prostate, uterus, ovary, bladder, and other solid tumors. Furthermore, if one of the four following conditions applies, then the RAC agrees that the EPA is warranted in modifying the BEIR VII methodologies. The four possible conditions are:

- 1) Information and data are needed about subject matter not addressed in BEIR VII;
- 2) More recent or more relevant data exist which could improve or otherwise influence the risk estimates;
- 3) Compelling evidence suggests the use of a more appropriate scientific method; or
- 4) The EPA’s implementation requirements for practicality or applicability necessitate an adaptation or other alternative to BEIR VII methodologies.

The RAC grouped all of the charge issues according to these conditions. For example, under condition one, the RAC considered prenatal exposures, bone and skin cancers, x- and alpha-particle radiations and tritium as areas not addressed by BEIR VII, and for which the EPA has a need to derive a basis for risk estimates. An example of applying condition two is that the use of the most recent Surveillance, Epidemiology, and End Results (SEER) data would improve the risk estimate. Examples of condition three are issues where a more appropriate scientific method was considered, i.e. in development of breast cancer risk estimates and the estimation of uncertainty. An example of condition four is the use of a stationary or a standard population.

The RAC concludes that the EPA’s use of the gray (Gy) as the unit of radiation absorbed dose is appropriate and agrees that modifying factors should be applied to the risk rather than dose.

The RAC’s approach to giving advice to the EPA is predicated on the basic premise that the risk estimates are for use in assessing population risk, rather than risk to a specific individual. This is because specific individuals may be more or less susceptible to radiation-induced cancer than the average for the population. Furthermore, at present there is little known about either the degree of or the causes of variation in individual susceptibility to the effects of radiation.

1                   **5. RESPONSE TO CHARGE QUESTION 2: WHITE PAPER**  
2                   **MODIFICATIONS AND EXTENSIONS**  
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4           **5.1 Response to Charge Question # 2**

5    *In addition to the overall approach described in BEIR VII, the draft White Paper presents*  
6    *specific modifications and extensions. Please comment on the soundness of the following*  
7    *proposals:*  
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- 9           a. *Calculation of the risk to the life table (stationary) population instead of the actual U.S.*  
10           *population (see Sections II.A.-C.); this is consistent with our current approach.*
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- 12           b. *Use of more recent incidence and mortality data from SEER and/or other sources (see*  
13           *Section II.D.); BEIR VII used a previous version of SEER data for the years 1995-1999.*  
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- 15           c. *Method for combining BEIR VII’s models for projecting risk from Japanese A-bomb*  
16           *survivors to U.S. population (see Section II.E.). In contrast to BEIR VII, we propose to*  
17           *combine the two risk models before integration to calculate the lifetime attributable risk.*  
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- 19           d. *Adoption of an alternative model for radiogenic lung cancer risk which may better*  
20           *account for the effects of smoking than the BEIR VII approach (see Section II.G.).*  
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- 22           e. *Method for calculating breast cancer mortality risk, accounting for the relatively long*  
23           *time from detection until death (see Section II.H.).*  
24
- 25           f. *Proposed approaches for extending risk estimates to radiations of different LET’s - in*  
26           *particular, deriving site-specific risk estimates for alpha or x radiations based on models*  
27           *derived from the A-bomb survivors, who were primarily exposed to gamma rays (see*  
28           *Section III).*  
29
- 30           g. *Estimation of risks for sites not specified in BEIR VII, specifically bone and skin, for*  
31           *which we propose to update our current approaches (see Sections III.A. and V,*  
32           *respectively).*  
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- 34           h. *Estimation of risk due to prenatal exposure. EPA’s current lifetime risk estimates do not*  
35           *include risk from prenatal exposure, and BEIR VII does not provide them. The draft*  
36           *White Paper uses ICRP recommendations to project its risks of childhood cancers*  
37           *induced by in utero exposure. Please comment on the soundness of the approach*  
38           *described in the draft White Paper to apply ICRP as described in Section IV.*  
39

1       **5.2    Response to Charge Question # 2a**

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3       *Calculation of the risk to the life table (stationary) population instead of the actual U.S.*  
4       *population (see Sections II.A.-C.); this is consistent with our current approach.*

5  
6       The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A.  
7       population using a standard stationary population based on the year 2000 death rate, or fixed  
8       cohort is a reasonable adaptation of the BEIR VII approach. Specifically, it avoids the potential  
9       for changes over time in the baseline cancer rates among the actual U.S.A. population that may  
10      be associated with changes in its racial, ethnic, cultural or other characteristics known to  
11      influence population disease rates. It also is consistent with the EPA’s established approach to  
12      cancer risk estimation from exposures to **chemicals (U.S. EPA. 2005a, U.S. EPA. 2005b, Also**  
13      **FR Vol 70, No. 66, pp 17765, April 7, 2005)**  
14

15      **5.3    Response to Charge Question #2b**

16  
17      *Use of more recent incidence and mortality data from SEER and/or other sources (see*  
18      *Section II.D.); BEIR VII used a previous version of SEER data for the years 1995-1999.*  
19

20      The RAC agrees that the EPA’s proposed use of the most current cancer-specific  
21      incidence and mortality rates available is an appropriate and scientifically valid adaptation of the  
22      BEIR VII approach.  
23

24      It is anticipated that incidence or mortality data for the years 1998-2002 will be available  
25      for the final calculations of radiogenic cancer incidence risk estimates from NCI’s SEER  
26      program. In contrast, only data from this program for 1995-1999 were available to BEIR VII.  
27

28      Although other potential sources of valid, nationally representative data will be  
29      considered by the EPA, the RAC considers that the most current SEER data are adequate and  
30      preferred for consistency with the BEIR VII approach. The EPA may want to consider the latest  
31      vital statistics report produced from the 2000 census for mortality rates if they become available  
32      before the final report is produced.  
33

34      **5.4    Response to Charge Question #2c**

35      *Method for combining BEIR VII’s models for projecting risk from Japanese A-bomb*  
36      *survivors to U.S. population (see Section II.E.). In contrast to BEIR VII, we propose to*  
37      *combine the two risk models before integration to calculate the lifetime attributable risk.*  
38

39      The RAC notes that there is considerable uncertainty in the application of risk estimates  
40      developed from the Japanese atomic bomb survivors to the U.S.A. population. This uncertainty  
41      results from different genetic and lifestyle characteristics of the two populations and differences

1 in the baseline cancer risks. The RAC agrees with the EPA’s proposed approach for projecting  
2 risk estimates from the Japanese A-bomb survivors to the U.S.A. population by combining the  
3 age-specific results from the Excess Absolute Risk (EAR) and Excess Relative Risk (ERR)  
4 models using the weighted geometric mean before calculating the lifetime attributable risk. This  
5 approach is a modification of that used in BEIR VII but is consistent with the method used  
6 previously by the EPA in FGR13. The RAC notes that the EPA method has the advantage of  
7 allowing the risk results from multiple exposures to be integrated, thereby enabling the risk from  
8 chronic lifetime exposure to be calculated.  
9

10 **5.5 Response to Charge Question #2d**

11 *Adoption of an alternative model for radiogenic lung cancer risk which may better account*  
12 *for the effects of smoking than the BEIR VII approach (see Section II.G.).*  
13

14 The RAC recommends that the EPA use the BEIR VII methodologies for deriving risk  
15 estimates for radiogenic lung cancer risk. The RAC does not find compelling evidence to  
16 suggest the use of the alternative model discussed by EPA.  
17

18 The lung cancer risk estimates reported by BEIR VII are primarily based on analyses of  
19 the LSS data. These estimates were not adjusted for cigarette smoking which is potentially an  
20 important confounder and/or effect modifier. This problem of lack of adjustment for cigarette  
21 smoking is further compounded by the fact that lung cancer incidence rates are lower in Japan  
22 than the U.S.A. and the lung cancer incidence rate ratio of males to females is considerably  
23 higher in Japan than in the U.S.A. The BEIR VII Committee was aware of this problem and  
24 chose to deal with it by using a risk transport model that more heavily weighted the EAR  
25 estimates relative to ERR estimates, i.e. assigning the weight of 0.7 for EAR and 0.3 for ERR.  
26 The BEIR VII Committee justified this approach based on mechanistic arguments and the  
27 finding reported by Pierce (Pierce et al. 2003), that in the LSS population of Japanese atomic  
28 bomb survivors the interaction between low LET radiation and smoking was consistent with an  
29 additive effect. This weighting scheme results in a Lifetime Attributable Risk (LAR) that is  
30 roughly twice as great among females as among males.  
31

32 The EPA white paper provided an alternative model to the BEIR VII lung cancer risk  
33 estimates. EPA was concerned that the lack of adjustment for cigarette smoking and birth cohort  
34 effects would result in an overestimate of risk in the U.S.A. population as well as female to male  
35 incidence rate ratio that was too high. EPA proposed to use a pure EAR model for lung cancer,  
36 equivalent to a weighting of 1.0 for EAR and 0.0 for ERR risk models.  
37

38 The RAC requested additional work on this problem from the EPA consisting of the  
39 following tasks:  
40

- 41 ● Compare results of the calculation of LAR using BEIR VII weighting to 100% EAR model  
42 and to alternative weighting schemes and/or the use of arithmetic, AM, or geometric, GM,  
43 means.  
44

- 1 ● Consider how the additive ERR model for smoking and radiation provides evidence for the  
2 appropriate weighting scheme.
- 3
- 4 ● Consider papers additional to Pierce (2003) on the nature of the smoking /radiation  
5 interaction.
- 6
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8 Based upon EPA’s response to these requests, Table 1 below illustrates the effect upon  
9 LAR estimates for lung cancer incidence of several different weighting schemes for the EAR and  
10 ERR risk models. The columns labeled White Paper (WP) and BEIR VII reflect differences in  
11 how the weighting was applied. BEIR VII used a weighted average of the final age-adjusted  
12 ERR and EAR estimates on a log scale, while EPA first weighted each age-specific stratum and  
13 then combined the weighted age-specific risk estimates. Inspection of the table reveals that the  
14 difference in application of the weights produced very small changes in the WP and BEIR VII  
15 LAR estimates. The weighting of 0.0 for ERR proposed by EPA produces LAR estimates that  
16 are somewhat smaller than the weight of 0.3 for ERR chosen by BEIR VII, most notably for  
17 females. The RAC also notes that the evidence for a purely additive model is not compelling  
18 based upon the literature review performed by EPA. There is some support for an interaction  
19 between radiation exposure and cigarette smoking that is intermediate between additive and  
20 multiplicative, similar to the weighting scheme selected by BEIR VII.

21  
22 Accordingly, due to a lack of compelling evidence to depart from the weighting approach  
23 used by BEIR VII, the RAC recommends that EPA should not employ alternative weighting  
24 schemes.

**Table 1: Comparison of the EPA White Paper (WP) and BEIR VII Method for Combining EAR and ERR LAR Projections for Lung Cancer Incidence.<sup>1</sup>**

	Combination Method RR weight <sup>2</sup> = 0.0		Combination Method RR weight <sup>3</sup> = 0.3		Combination Method RR weight = 0.5		Combination Method RR weight = 0.7		Combination Method RR = 1.0	
	WP	BEIR VII	WP	BEIR VII	WP	BEIR VII	WP	BEIR VII	WP	BEIR VII
<b>Sex</b>										
<b>Male</b>	179	179	186	193	195	203	206	213	230	230
<b>Female</b>	344	344	401	428	460	495	541	573	714	714

NOTE: Number of cases per 100,000 persons exposed to 0.1 Gy. Results do not incorporate DDREF adjustment.

<sup>1</sup>Results are shown for stationary populations and SEER incidence data for the years 1998-2002.

<sup>2</sup>Weight for projection based on EPA proposal

<sup>3</sup>Weight for projection using BEIR VII

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**5.6 Response to Charge Question #2e**

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

The RAC notes that the EPA adopts BEIR VII’s approach to estimating the risk of breast cancer in females that differs from that used by BEIR VII to estimate the risks for the majority of other solid cancers. However, the EPA identified issues relative particularly to the changing clinical course of breast cancer in conjunction with a relatively long survival period, and questions some aspects of BEIR VII’s risk estimation method for this site-specific cancer. The EPA thus has identified several alternative methods for estimating the relative risk for radiogenic breast cancer in an effort to take into account some of the temporal features that can influence the cancer’s clinical course and hence the risk estimates. The RAC concurs with the EPA’s decision to explore these alternative methods.

Specifically, the RAC concurs with the EPA’s proposal to relate current breast cancer mortality rates to retrospective incidence rates rather than current incidence rates to better reflect the influence of life style changes, earlier breast cancer detection and treatment that could influence survival and hence mortality rates over an extended period.

The RAC notes the potential for development of second cancers during the cancer survival period. Such an event could be spontaneous or related to treatment of the initial cancer. In the case of breast cancer, it could impact mortality reporting and loss of deaths attributed to breast cancer.

The RAC suggests that the EPA explore the feasibility of using the BEIR VII approach with the proposed method (above) with retrospective lagging incidence rates relative to current mortality rates.

**5.7 Response to Charge Question #2f**

*Proposed approaches for extending risk estimates to radiations of different LET’s - in particular, deriving site-specific risk estimates for alpha or x radiations based on models derived from the A-bomb survivors, who were primarily exposed to gamma rays (see Section III).*

A significant extension requiring subject matter not addressed in BEIR VII is guidance on how to deal with the estimation of risks from exposures to different LET radiation, especially alpha particles and lower energy photons and beta particles. Knowledge of these risks is required particularly for dealing with the possible health risks from chronic irradiation from alpha, beta, or gamma emissions from internally deposited radionuclides. A key feature of the low-LET radiation exposures used in the analyses available in the BEIR VII report, especially

1 those based on the Japanese atomic bomb survivors, is that they involved a very brief, whole-  
2 body exposure to radiation from an external source. In such a situation, all of the organs and  
3 tissues of the body were irradiated and the long-term risks to these organs and tissues have been  
4 studied directly. When dealing with internally deposited radionuclides, the situation is different  
5 because the radionuclide is likely to be distributed non-uniformly in the body, with only a few  
6 organs and tissues receiving most of the dose. This can change the spectrum of cancers  
7 produced. Also, because of the possible long-term retention of some long-lived radionuclides,  
8 the dose can continue to accumulate at a low dose rate over months or years. Dealing with these  
9 differences is important but not necessarily straightforward as discussed below.

## 10 11 **Higher LET Radiation**

12  
13 The RAC noted that the white paper only considered alpha particles for radionuclides  
14 inhaled or ingested.

### 15 16 **A. Alpha Particles**

17  
18 The EPA white paper discusses three possible approaches to estimating the lifetime  
19 health risks from internally deposited alpha-emitting radionuclides. These three approaches are  
20 discussed below:

#### 21 22 a) Data from human populations exposed to alpha-emitting radionuclides.

23  
24 Good risk data are available for the following organs and tissues (U.S. NAS/NRC. 1988;  
25 U.S. NAS/NRC. 1999; Koshurnikova et al. 2000; Gilbert et al. 2004):

- 26 - Bone cancer from radium dial painters and radium chemists exposed to  $^{226,228}\text{Ra}$ ;
- 27 - Bone Cancer from ankylosing spondylitis patients exposed to  $^{224}\text{Ra}$ ;
- 28 - Liver cancer from patients given Thorotrast ( $^{232}\text{Th}$ ) as an imaging agent;
- 29 - Leukemia from patients given Thorotrast ( $^{232}\text{Th}$ ) as an imaging agent;
- 30 - Lung cancer from uranium miners who inhaled  $^{222}\text{Rn}$  and progeny; and
- 31 - Lung cancer from Mayak Russian workers who inhaled  $^{239}\text{Pu}$ .

32  
33 Since the lung, liver, bone and bone marrow are the major organs at risk for internally  
34 deposited, alpha-emitting radionuclides, these populations provide important information on  
35 carcinogenic risk for alpha-emitting radionuclides. The RAC notes that this information is based  
36 on site-specific cancer mortality among groups whose total doses are generally well above the  
37 low-dose region.

#### 38 39 b) Data from life-span studies of laboratory animals exposed via various routes of exposure 40 to graded activity levels of alpha-emitting radionuclides.

41  
42 There are sizeable data bases available for different species of laboratory animals  
43 exposed to different beta-, gamma- or alpha-emitting radionuclides by various routes and studied  
44 for their lifetimes. These studies provide much information on the life-span health effects but the  
45 number of variables involved including species, route of exposure, animal husbandry and other  
46 factors make it difficult to extrapolate the risk results directly to human populations in a

1 consistent manner. However, they do provide useful information on radionuclides for which no  
2 human data are available. Such studies also help define the influence of dose distribution and the  
3 relative effectiveness of high- and low-LET radiations in those cases where studies of the high  
4 and low-LET emissions were examined in a parallel manner under similar conditions.

5  
6 c) The most recent cancer risk data from the RERF studies of atomic bomb survivors  
7 exposed to low-LET radiation multiplied by a general  $RBE_M$  factor for alpha particles.  
8

9 This third, more general, approach assumes that an appropriate value for  $RBE_M$  is known  
10 and that it is appropriate to use this value with the cancer risk seen after a brief, high dose-rate  
11 exposure received by the atomic bomb survivors to estimate cancers risks in a broad range of  
12 organs and tissues for which no data are available for alpha-particle exposure.  
13

14 As discussed in Section III.A.3, Summary and Recommendations of the White Paper, the  
15 EPA proposes to multiply site-specific gamma-ray cancer risk estimates by an RBE of 20 to  
16 derive corresponding estimates of cancer risk from alpha radiation, with two exceptions:  
17

- 18 a) An RBE = 1-3 for leukemia induced by alpha emitters deposited in bone; and  
19 b) Continued use of models derived from BEIR VI to estimate lung cancer risk from  
20 inhaled radon progeny.  
21

22 The RAC recognizes the problems that the EPA has to deal with in adding consideration  
23 of alpha-emitting radionuclides to the information already provided for low-LET radiation in the  
24 BEIR VII report. This particular issue is one example of the need for a practical, operational  
25 public health approach to radiation protection and standards setting mentioned earlier in this  
26 Advisory. On this basis, the RAC is supportive of the use of a generally accepted  $RBE_M$  value  
27 such as the 20 that they are using currently. For those radionuclides for which human cancer risk  
28 data are available for the lung, liver, bone, or bone marrow, the RAC recommends that this  
29 information be used directly whenever possible. For other organs and tissues, the RAC is  
30 supportive of the general approach (except for bone cancer as discussed in Section 5.8) of using  
31 the low-LET cancer risk from BEIR VII multiplied by  $RBE_M$ .  
32

### 33 **B. Low-energy Photons and Electrons**

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35 The EPA White Paper suggests that the relative biological effectiveness (RBE) for  
36 medical x rays is about 2 – 2.5. However, x-rays are not uniquely different from gamma-rays  
37 except for their production. Any risk estimate associated with exposure to photons needs to be  
38 correlated with the energy of the photon rather than the method of production.  
39

40 Reviews by ICRU (1986) and Kocher et al. (2005) show that RBEs for low energy  
41 photons, < 30 keV, and low energy electrons, <15 keV, are higher than one when compared to  
42 higher energy x-rays and  $^{60}\text{Co}$  gamma-rays. A probability distribution by Kocher et al. (2005)  
43 showed a median radiation effectiveness factor of approximately 2.4 for photons less than 30  
44 keV and for  $^3\text{H}$  beta particles. Thus, an effectiveness factor for these low energy radiations in  
45 the range of 2 to 2.5 seems reasonable.

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**5.8 Response to Charge Question #2g**

*Estimation of risks for sites not specified in BEIR VII, specifically bone and skin, for which we propose to update our current approaches (see Sections III.A. and V, respectively).*

The risk of bone cancer from low-LET radiation is not specified in the BEIR VII report but such information is required to consider the cancer risk from a bone-seeking beta-emitting radionuclide such as <sup>90</sup>Sr. In this case, the EPA proposes to do the reverse of what is discussed above in Section 2f. Instead of multiplying a low-LET cancer risk by an RBE to estimate a high-LET cancer risk, it proposes to divide the bone cancer risk observed in humans exposed to alpha particles from <sup>224</sup>Ra by an RBE to estimate the bone cancer risk from <sup>90</sup>Sr (NCRP 1991). Once again, this practical, operational approach to radiation protection and standards setting seems appropriate and conservative for the task at hand.

The RAC recognizes that although the BEIR VII committee chose not to provide risk estimates for non-melanoma skin cancer (NMSC) induced by ionizing radiation, EPA has an operational need for such estimates. This presents ORIA with certain methodological challenges given the high incidence and low mortality rates of NMSC among the US general population and the limitations of available data.

The RAC supports EPA's proposed use of the 1991 ICRP model to estimate the incidence and mortality risks of radiogenic NMSC taking into account more recent findings that most of the NMSCs attributable to low to moderate doses of LET ionizing radiation are of the basal cell carcinoma (BCC) type (Shore. 2001.), and that the incidence rates of BCC have been increasing substantially in recent decades among the general population (Karagas et al. .1999.).

However, the RAC concurs with EPA that because of the high background incidence rates and low mortality due to NMSC, it is inappropriate to include risk estimates for radiogenic NMSC in the estimate of the total risk for radiogenic cancer. The RAC also notes that as ionizing radiation is not considered to be a risk factor for melanoma skin cancer there is no rationale for risk estimation in this instance.

**5.9 Response to Charge Question #2h**

*Estimation of risk due to prenatal exposure. EPA’s current lifetime risk estimates do not include risk from prenatal exposure, and BEIR VII does not provide them. The draft White Paper uses ICRP recommendations to project its risks of childhood cancers induced by in utero exposure. Please comment on the soundness of the approach described in the draft White Paper to apply ICRP as described in Section IV.*

1 BEIR VII does not provide risk estimates for *in utero* exposure to radiation. Even though  
2 the risk from *in utero* exposure is a minor component of the overall radiogenic cancer risk, the  
3 EPA requires an estimate for radiation protection and standard setting purposes.  
4

5 Few human data exist on which to base an estimate of radiogenic cancer risk for *in utero*  
6 exposure to radiation from either external sources or internally deposited radioactive materials.  
7

8 The primary sources of data for external exposures are the Oxford Survey of Childhood  
9 Cancer (Stewart et al., 1958.; Mole, 1990) and as reviewed by Mettler and Upton, (1995) and by  
10 Doll and Wakefield, (1997) and the studies of Japanese atomic bomb survivors exposed in utero  
11 (Delongchamp et al., 1997). When all sources of uncertainty are taken into account, the risk  
12 estimates from these studies are not incompatible with each other (Wakeford & Little, 2002).  
13

14 The dose to the embryo/fetus from internally-deposited radionuclides has been reviewed  
15 (NCRP, 1998; ICRP 2000) and ICRP (2001) provides organ/tissue dose coefficients (Sv/Bq) to  
16 the embryo/fetus from chronic intake of individual radionuclides by the mother. These data can  
17 be used to develop cancer risk estimates for the embryo/fetus exposed coincidentally to radiation  
18 delivered at low dose rates from the same sources  
19

20 The RAC concludes that it would be reasonable for the EPA to use the dose coefficients  
21 provided by ICRP as a basis for developing its estimates risk estimates for *in utero* radiation  
22 exposure from internally-deposited radionuclides.  
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## 6. RESPONSE TO CHARGE QUESTION 3: UNCERTAINTIES NOT QUANTIFIED IN BEIR VII

**Charge Question 3:** *BEIR VII provides quantitative uncertainty bounds for each of its risk coefficients. EPA proposes to adopt this methodology with some additional discussion of the uncertainties not quantified in BEIR VII. Please comment on the adequacy of this approach (see Section II.K.).*

The RAC strongly endorses the EPA-ORIA’s desire to estimate uncertainty bounds for its radiogenic cancer risk estimates. Indeed, given the range of possible operational uses of the risk estimates, as much effort should go into estimating the uncertainty bounds as into producing the central or point risk estimates themselves.

Ideally, the uncertainty analysis would involve the development of a probability density function for (site-specific) estimated risk, rather than bounds around a central or point risk estimate. Such an approach, which has previously been considered by other national and international committees, would facilitate risk estimation based on other than the average risk. For example, such an approach might facilitate the identification of a minimum cost-of-errors (or ‘loss’) risk estimate for operational use (e.g., in risk-informed regulation). However, the RAC believes that such an approach is not likely to be practically achievable, and endorses the EPA-ORIA’s approach (central risk estimate with uncertainty bounds, following BEIR VII).

The uncertainty bound estimates should incorporate, to the extent possible, all sources of error and/or uncertainty, including the three main sources identified in BEIR VII (sampling variability in the LSS data, transport of risk from LSS to the U.S.A. population, and the appropriate value for DDREF at both high and low doses of low-LET radiation (or, equivalently, the appropriate use of the LNT dose-response model used for low dose extrapolation)). Other sources of error and/or uncertainty identified by the EPA-ORIA (including dosimetry (of which neutron RBE is a factor), disease detection, disease classification, temporal patterns, and appropriate RBE values) should also be considered.

By “consider,” the RAC means that the EPA-ORIA should attempt to estimate, in a preliminary fashion, the relative magnitude of the contribution of the additional known sources of error or uncertainty they identified to the overall uncertainty. Of importance, it is useful to try to estimate the independent contribution of these additional sources, most of which are likely partially correlated with those sources identified in BEIR VII. One possible way of estimating the magnitudes is via some modest simulation studies. Only if the independent contribution of any of these additional sources of error is potentially significant in magnitude should that source be included in the uncertainty analysis. In any event, the methods of uncertainty analysis should follow BEIR VII.

There is some value to producing two sets of uncertainty bounds, one representing the bounds on the (site-specific) central or point risk estimate for the method of combining the RR and AR that the EPA finally chooses to use, the other representing combinations ranging from 100% RR through 100% AR. The former gives a measure of the uncertainty of the central risk

1 estimate derived from the method specifically used, and the latter gives an indication of the range  
2 in which the true value (independent of method) likely resides.

3  
4 In coming to these recommendations, the RAC considered several additional  
5 complications that could influence uncertainty. One such complication arises because the  
6 uncertainties associated with the current risk estimates for radiogenic cancers are smallest for the  
7 doses at which statistically significant increases in cancer mortality or incidence have been  
8 observed in the LSS and other epidemiological studies of exposed populations. However, such  
9 increases have been observed over a limited range of individual doses. At doses below this  
10 range, risk estimates are based, on an assumed LNT dose-response model and method of  
11 extrapolation from higher-dose/higher-response data. This extrapolation may result in the risk  
12 estimates associated with doses in the low-dose range having larger relative uncertainties than  
13 those in the higher dose range.

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15  
16 Having said that, BEIR VII specifically considered adaptive response, genomic  
17 instability, and bystander effects, and concluded that there is insufficient evidence to explicitly  
18 add these effects to the dose-response model. The EPA-ORIA proposes at the present time to  
19 follow BEIR VII and use the LNT combined with the DDREF for calculation of radiation risk.  
20 In the absence of compelling scientific evidence to do otherwise, the RAC endorses the EPA-  
21 ORIA’s plan in this regard. The RAC does recommend, however, that the EPA-ORIA include a  
22 (qualitative) discussion of modern cellular and molecular biological concepts in its final report.  
23 As a cautionary note, the RAC recommends that the EPA discuss the application of its LNT risk  
24 estimates in very low dose settings where currently cancer risks are not significantly elevated  
25 above background cancer rates and where the doses are a fraction of the background radiation  
26 exposure.

27  
28 It is important to note that there is indeed opportunity to include uncertainties in the  
29 model – that is, uncertainties in high-dose versus low dose behavior – in the overall uncertainty  
30 analysis. In BEIR VII and the EPA-ORIA’s proposed approach to uncertainty estimation, this  
31 “additional” uncertainty is contained within the uncertainty in the value for DDREF, since  
32 DDREF is only invoked at lower doses. The RAC thus strongly endorses the EPA-ORIA’s  
33 intention to include uncertainty in DDREF in the overall uncertainty analysis.

34  
35 There is also a need to evaluate uncertainty following exposure to high doses delivered at  
36 low dose rates. In addition to the DDREF it may be necessary to have a dose rate effectiveness  
37 factor for high doses delivered at low dose rates. Low dose rate exposure causes minimal life  
38 shortening even when the total doses are very large. The cancer risk estimates derived for acute  
39 exposure even with a DDREF do not result in an accurate prediction of risk to populations  
40 exposed to high doses delivered at a low dose rate.

41  
42 Uncertainties in the estimates are also a function of time into the future, being smallest in  
43 the near time frame. This is due to several factors, including changes in future (actual)  
44 populations (as opposed to a ‘stationary population’), future background cancer incidence, and  
45 future medical advances (since the case fatality rate may decrease as a result of better treatment  
46 interventions in the future). Uncertainties thus become greater as the risk estimates are applied

1 further into the future. The RAC recommends that EPA-ORIA include a (qualitative) discussion  
2 of these concepts in its final report.  
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**7. RESPONSE TO CHARGE QUESTION 4: ISSUES RELATING TO RADIOGENIC THYROID CANCER NOT QUANTIFIED IN BEIR VII**

**Charge Question 4:** *In Section VI, the draft White Paper discusses some issues relating to radiogenic thyroid cancer. Does the RAC have any specific suggestions for dealing with this risk; e.g., does the RAC have any advice on gender specificity, effectiveness of iodine -131 compared to gamma rays, or estimation of thyroid cancer mortality?*

The RAC believes that it is premature to offer any advice to ORIA on this issue. A major review of radiogenic thyroid cancer is being completed by the National Council on Radiation Protection and Measurements. This information should be considered by ORIA as more recent or more relevant data which could improve the risk estimates provided by BEIR VII.

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## 8. ISSUES BEYOND THE CHARGE

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4           The RAC received information from the public on the use of “Reference Man” for setting  
5 radiation protection standards. The RAC recommends the EPA consider the concept described  
6 in ICRP Publication 89 (ICRP. .2002.). In ICRP 89, this concept has been expanded into what  
7 might be thought of as a Reference Family because it contains reference information on persons  
8 at ages from newborns to adults and both genders. It also looks at results from studies of Asian  
9 reference persons.

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(Format citation will be finalized in later draft- - - KJK)

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1 **APPENDIX A –ON-GOING RESEARCH AND PARADIGMS**  
2 **ASSOCIATED WITH BIOLOGICAL RESPONSES TO LOW DOSES OF**  
3 **RADIATION**

4  
5 According to the BEIR VII report, “Atomic bomb data for solid tumors combined  
6 provide statistical evidence of a radiation-associated excess at doses down to around 100 mSv;  
7 these combined data are well described by a linear no-threshold dose-response, although some  
8 low dose nonlinearity is not excluded (US NAS/NRC. 2006. BEIR VII, p. 245).” “It is  
9 abundantly clear that direct epidemiological and animal approaches to low dose cancer risk are  
10 intrinsically limited in their capacity to define possible curvilinearity or dose thresholds for risk  
11 in the range of 0-100 mSv. For this reason the present report has placed much emphasis on the  
12 mechanistic data that can underpin such judgments (US NAS/NRC. 2006. BEIR VII, p.245).”  
13

14 The uncertainty associated with the use of the epidemiological data to estimate risk in the  
15 low dose range has been covered in detail in Charge Question 3: Uncertainties not Quantified in  
16 BEIR VII. An additional source of uncertainty in risk estimates is associated with the  
17 mechanistic biophysical model that is used in BEIR VII to support the LNT in the low dose  
18 region. Although the BEIR VII committee conducted an extensive review of the cell and  
19 molecular literature relative to biological responses at low doses and discussed the recent  
20 advances, they concluded that the mechanistic cell and molecular biological research supported  
21 the current biophysical model that they use (US NAS/NRC. 2006. BEIR VII, pp. 63-64).  
22 However, the rapid increase in information on the biological responses to low doses of radiation  
23 suggest new paradigms in radiation biology (Brooks 2005) that may modify the biophysical  
24 model used in the BEIR VII report.  
25

26 BEIR VII uses a biophysical model that suggests that each and every ionization increases  
27 the probability of a DNA breakage (Burma et al. 2001) and that this results in a linear increase in  
28 the risk for mutations and therefore in the risk for cancer (US NAS/NRC. 2006. BEIR VII, pp.  
29 10-11). This model assumes independent action of cells and a lack of cell communication. The  
30 model suggests that there is no change in response as a function of previous radiation exposure  
31 and that there is a linear link between unrepaired DNA damage, rare mutational events and the  
32 development of cancer. Recent research has been conducted to provide a solid data base on the  
33 response of molecules, cells, tissues and organisms to very low doses and dose rates of radiation  
34 (Ko et al. .2004.; Azzam and Little .2004.; Little .2006.; Brooks .2005.; Mitchel et al. .2004.).  
35 This research has suggested that several of the assumptions used in the BEIR VII biophysical  
36 model may no longer be valid (Tubiana 2005). The data base that questions the assumptions  
37 used by BEIR VII include information on dose dependent changes in gene expression, radiation  
38 induced changes in redox status of the cells, apoptosis, bystander effects, adaptive responses, and  
39 genomic instability (Spitz et al. .2004; Di Masi et al. .2006.; Coleman et al. .2005.; Azzam and  
40 Little .2004.; Little .2006.; Brooks .2004.). The BEIR VII report has discussed each of these  
41 effects and concluded that until molecular mechanisms of action involved in the induction of low  
42 dose biological effects are elucidated, they cannot be utilized in modification of dose-response  
43 relationships. This appendix provides a brief review on the mechanistic research being  
44 conducted and to suggest the need for continuously updating the biophysical model used to  
45 support the estimates of radiation risk following low dose radiation exposure.

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It is well known that cells communicate by a variety of direct and indirect mechanisms. Many new radio-biological observations indicate that cells do not respond to radiation independently. This communication results in modification of responses to low dose and dose rate radiation.

Using recently developed microbeams and other technology to expose individual cells and study the response of the “hit” cells and the response of neighboring cells demonstrated the presence of “bystander effects.” These effects demonstrate that a cell traversed by an alpha particle or “hit” by a focused low LET beam communicate with neighboring cells and can produce changes in “non-hit” cells. These changes have been shown to be both “harmful” and “protective” and are most marked following exposure to high-LET radiation (Little 2006.). Bystander effects impact the current use of “hit-theory” in defining radiation risk since the radiation target is much larger than the individual cell. The research demonstrates that cells communicate within each tissue making the assumption of independence of action of individual cells used in the BEIR VII biophysical model inappropriate. Since non-hit cells show biological responses, it may not be appropriate to calculate radiation dose to individual cells or cell types in tissues. (US NAS/NRC. 2006. BEIR VII page 54) Bystander effects also make it more difficult to define the biological target for the interaction of radiation with cells and the induction of cancer. The data suggest that tissues and organs respond as a whole and that the biological response is related to the dose to the whole organ/tissue which is the metric used by BEIR VII in all the human studies rather than to the dose to individual cells (Barcellos-Hoff and Brooks .2001.).

It has been demonstrated that following exposures to low doses of radiation there are unique dose-dependent changes in gene and protein expression which were not recognized or identified when the BEIR VII biophysical models were developed (Ding et al. 2005.; Coleman and Wyrobek 2006.; Marchetti et al. 2006.). Low dose activation of such mechanisms supports the existence of non-linear dose-response relationships for low-LET radiation. Identification of these genes is providing a scientific basis for defining metabolic pathways activated by radiation and determining mechanisms of action.

Previous radiation exposure can alter the response producing diminished biological effects. This is called the “adaptive response”. Two different types of adaptive responses have been identified (Azzam and Little 2004.). The first is where low doses of radiation decrease the amount of damage observed relative to background levels (Ko et al. 2006.). The second is where a small “priming dose” of radiation given before a high acute “challenge dose” results in a decreased response relative to the high dose alone (Olivieri et al .1984.). The ability to produce an adaptive response is dependent on genetic background of the cells. Different sets of genes are up and down regulated in cells capable of adaptation compared to cells that cannot adapt to radiation exposure. Cells and tissues that demonstrate an adaptive response following low dose exposures have repair and stress genes up regulated (Coleman et al. 2005.).

Research has been conducted to understand cell/cell and cell/tissue interactions and how they modify cancer frequency (Barcellos-Hoff 2005.). Tissue interactions have been shown to modify the expression of cellular and molecular damage and to be critical in the expression of

1 cancer. There is evidence that under certain experimental conditions, radiation damage can be  
2 modified *in vitro* (Kennedy et al. 2006). Also administration of stable iodine considerably later  
3 than the period normally prescribed to block exposure to radioactive iodine was unexpectedly  
4 associated with a decreased risk of thyroid cancer incidence among a population at risk of  
5 exposure as a result of the Chernobyl accident. The authors suggested that this finding may be  
6 related to a modification of radiation-induced cellular or molecular damage in the presence of  
7 stable iodine (Cardis et al. 2005). Data from this research verified that the initial DNA damage  
8 increases linearly with radiation dose, that DNA damage triggers many molecular responses and  
9 that even the initial DNA damage and repair is modified by radiation type, dose and dose-rate  
10 (Ishizaki et al. 2004.). Importantly, it has shown that biological repair of this damage as well as  
11 the other cellular and organ responses are very non-linear over the low dose region. These new  
12 findings may have significance in quantifying the safety margins associated with regulatory  
13 standards.

14  
15 Genomic instability suggests that, in addition to rare mutational events, frequent  
16 radiation-induced changes following exposure may play an important role in cancer induction.  
17 Radiation-induced genomic instability is seen at a high frequency in cells many cell divisions  
18 after the radiation exposure (Morgan 2003.; Ponnaiya et al. 1997.). The instability results in  
19 increased frequency of mutations, chromosome aberrations, and cell killing. Radiation-induced  
20 genomic instability seems to be one of the early stages in the carcinogenesis process and has  
21 been seen both *in vitro* and *in vivo*. These observations challenge the relative importance that  
22 initial mutations play in radiation-induced cancer (Kadhim et al. 2004.). The BEIR VII  
23 biophysical model suggests that since DNA damage increases as a linear function of acute  
24 radiation dose that there must be a linear increase in cancer risk (page reference). Genomic  
25 instability and the ability to modify responses after the radiation exposure both challenge the  
26 linear relationship between initial DNA damage and cancer frequency.

27  
28 The magnitude of the response for all of these phenomena has been shown to be  
29 dependent on the genetic background of the cells, tissues and organisms in which they are being  
30 measured (Coleman et al. 2005.; Ponnaiya et al. 1997.; Azzam and Little 2004.; Little 2006.). A  
31 better definition of the range of inter-individual variability and the development of analytical  
32 methods and tools may make it possible to identify individuals that are either sensitive or  
33 resistant to either the early or late effects of radiation or both. However, currently it is not  
34 possible to identify either radiation resistant or radiation sensitive individuals, or to use this  
35 information in a regulatory framework.

36  
37 These recent advances provide a scientific basis for the observed non-linear dose-  
38 response relationships seen in many biological systems (US NAS/NRC. 2006. BEIR VII; Ko et  
39 al. 2006.; Mitchel et al. 2004.). They suggest that the mechanism of action of radiation-induced  
40 damage is different following exposure to high doses than it is after low radiation doses. It  
41 becomes important to consider new paradigms associated with the biological responses to low  
42 doses of radiation and to modify and further develop the models used to support the  
43 extrapolation of dose-response relationships into dose regions where it is not possible to measure  
44 changes in radiation-induced cancer incidence/mortality in human populations.

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**APPENDIX B – BIOSKETCHES**

**U.S. ENVIRONMENTAL PROTECTION AGENCY  
SCIENCE ADVISORY BOARD  
RADIATION ADVISORY COMMITTEE (RAC)**

--- (To be Added in Quality Review Draft) ---

## APPENDIX C – ACRONYMS

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2		
3	A-Bomb	<u>A</u> tom <u>B</u> omb
4	AM	<u>A</u> rithmet <u>M</u> ean
5	AR	<u>A</u> bsolut <u>R</u> isk
6	BCC	<u>B</u> asal <u>C</u> ell <u>C</u> arcinoma
7	BEIR	<u>B</u> iological <u>E</u> ffects of <u>I</u> onizing <u>R</u> adiation
8	BEIR VII	<i>Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII</i>
9		<i>Phase 2</i>
10	CDC	<u>C</u> enters for <u>D</u> isease <u>C</u> ontrol and Prevention
11	CFR	<u>C</u> ode of <u>F</u> ederal <u>R</u> egulations
12	Co	Chemical symbol for cobalt ( <sup>60</sup> Co isotope)
13	DDREF	<u>D</u> ose and <u>D</u> ose- <u>R</u> ate <u>E</u> ffectiveness <u>F</u> actor
14	DFO	<u>D</u> esignated <u>F</u> ederal <u>O</u> fficer
15	DNA	<u>D</u> eoxyribonucleic <u>A</u> cid
16	EAR	<u>E</u> xcess <u>A</u> bsolut <u>R</u> isk
17	EPA	<u>E</u> nvironmental <u>P</u> rotection <u>A</u> gency (U.S. EPA)
18	ERR	<u>E</u> xcess <u>R</u> elativ <u>R</u> isk
19	FR	<u>F</u> ederal <u>R</u> egister
20	FGR-13	Federal <u>G</u> uidance <u>R</u> eport <u>13</u>
21	GM	<u>G</u> eometric <u>M</u> ean
22	GMC	<u>G</u> eometric <u>M</u> ean <u>C</u> oefficient
23	GSD	<u>G</u> eometric <u>S</u> tandard <u>D</u> eviation
24	Gy	gray
25	H	Chemical symbol for <u>H</u> ydrogen ( <sup>3</sup> H isotope)
26	I	Chemical symbol for <u>I</u> odine ( <sup>131</sup> I isotope)
27	ICRP	<u>I</u> nternational <u>C</u> ommission on <u>R</u> adiological <u>P</u> rotection
28	ICRU	<u>I</u> nternational <u>C</u> ommission on <u>R</u> adiation <u>U</u> nits and Measurements, Inc.
29	IREP	<u>I</u> nteractive <u>R</u> adio <u>E</u> pidemiological <u>P</u> rogram
30	keV	<u>k</u> ilo <u>e</u> lectron <u>V</u> olts
31	LAR	<u>L</u> ifetime <u>A</u> ttributible <u>R</u> isk
32	LET	<u>L</u> inear <u>E</u> nergy <u>T</u> ransfer
33	LNT	<u>L</u> inear <u>N</u> on <u>T</u> hreshold
34	LSS	<u>L</u> ife <u>S</u> pan <u>S</u> tudy
35	mSv	<u>m</u> illi- <u>S</u> ievert
36	NAS	<u>N</u> ational <u>A</u> cademy of <u>S</u> ciences (U.S. NAS)
37	NCHS	<u>N</u> ational <u>C</u> enter for <u>H</u> ealth <u>S</u> tatistics
38	NCI	<u>N</u> ational <u>C</u> ancer <u>I</u> nstitute
39	NCRP	<u>N</u> ational <u>C</u> ouncil on <u>R</u> adiation <u>P</u> rotection and Measurements
40	NIH	<u>N</u> ational <u>I</u> nstitutes of <u>H</u> ealth
41	NIOSH	<u>N</u> ational <u>I</u> nstitute for <u>O</u> ccupational <u>S</u> afety and <u>H</u> ealth
42	NMSC	<u>N</u> on- <u>M</u> elanoma <u>S</u> kin <u>C</u> ancer
43	NRC	<u>N</u> ational <u>R</u> esearch <u>C</u> ouncil
44	OAR	<u>O</u> ffice of <u>A</u> ir and <u>R</u> adiation (U.S. EPA/OAR)
45	ORIA	<u>O</u> ffice of <u>R</u> adiation and <u>I</u> ndoor <u>A</u> ir (U.S. EPA/OAR/ORIA)

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2	PAG	<u>P</u> rotective <u>A</u> ction <u>G</u> uide
3	Pu	Chemical symbol for <u>P</u> luto <u>n</u> ium ( <sup>239</sup> Pu Isotope)
4	QA	<u>Q</u> uality <u>A</u> ssurance
5	QC	<u>Q</u> uality <u>C</u> ontrol
6	QA/QC	<u>Q</u> uality <u>A</u> ssurance/ <u>Q</u> uality <u>C</u> ontrol
7	R	<u>r</u> oentgen
8	Ra	Chemical symbol for <u>R</u> adium (Isotopes include <sup>224</sup> Ra, <sup>226</sup> Ra, <sup>228</sup> Ra, and <sup>236</sup> Ra)
9	RAC	<u>R</u> adiation <u>A</u> dvisory <u>C</u> ommittee (U.S. EPA/SAB/RAC)
10	rad	Traditional unit of <u>r</u> adiation absorbed dose in tissue (a dose of 100 rad is
11		equivalent to 1 gray (Gy) in SI units)
12	RBE	<u>R</u> elative <u>B</u> iological <u>E</u> ffectiveness
13	RBE <sub>m</sub>	Maximum <u>R</u> elative <u>B</u> iological <u>E</u> ffectiveness
14	REF	<u>R</u> adiation <u>E</u> ffectiveness <u>F</u> actor
15	rem	<u>R</u> adiation equivalent in <u>m</u> an; traditional unit of effective dose equivalent (equals
16		rad x tissue weighting factor) (100 rem is equivalent to 1 Sievert (Sv))
17	RERF	Radiation Effects Research Foundation
18	R/h	<u>R</u> oentgen per <u>h</u> our; traditional measure of exposure rate
19	Rn	Chemical symbol for Radon ( <sup>222</sup> Rn Isotope)
20	RR	<u>R</u> elative <u>R</u> isk
21	SAB	<u>S</u> cience <u>A</u> dvisory <u>B</u> oard (U.S. EPA/SAB)
22	SCC	<u>S</u> quamous <u>C</u> ell <u>C</u> arcinoma
23	SEER	<u>S</u> urveillance, <u>E</u> pidemiology, and <u>E</u> nd <u>R</u> esults
24	SI	<u>I</u> nternational <u>S</u> ystem of <u>U</u> nits (from NIST, as defined by the General Conference
25		of Weights & Measures in 1960)
26	Sr	Chemical Symbol for <u>S</u> trontium ( <sup>90</sup> Sr Isotope)
27	Sv	<u>s</u> ievert, SI unit of effective dose equivalent in man (1 Sv is equivalent to 100 rem
28		in traditional units)
29	Th	Thorotrast ( <sup>232</sup> Th Isotope)
30	UNSCEAR	<u>U</u> nited <u>N</u> ations <u>S</u> cientific <u>C</u> ommittee on the <u>E</u> ffects of <u>A</u> tom <u>i</u> c <u>R</u> adiation
31	US	<u>U</u> nited <u>S</u> tates
32	WLM	<u>W</u> orking <u>L</u> evel <u>M</u> onths

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