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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
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- - - Quality Review Draft - - -

EPA-SAB-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 EPA 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 from exposure to low levels of ionizing radiation. 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 as recommended by 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.

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, other solid cancers, and leukemia. 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.

There were several areas not addressed by BEIR VII, for which EPA requires a cancer risk estimate. They include:

- ***in utero*** - The RAC concludes that it would be reasonable for the EPA to use the referenced estimates of cancer risk from *in utero* exposure to external radiation sources, and the dose coefficients provided by the ICRP as a basis for developing its risk estimates for *in utero* radiation exposure from internally-deposited radionuclides.
- **Bone** - The EPA proposes to divide the bone cancer risk observed in humans exposed to alpha particles from ^{224}Ra by an RBE to estimate the bone cancer risk from ^{90}Sr. The RAC concurs with this practical, operational approach to radiation protection.
- **non-melanoma skin cancer (NMSC) -** 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. The RAC concurs with EPA that because of the high baseline incidence rates and low mortality due to NMSC, it is inappropriate to include risk estimates for radiogenic NMSC in the estimate of the incidence and mortality risk for radiogenic cancer.
- **higher LET radiation**
    - **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. The RAC recommends using data specific to particular radionuclides where such human cancer risk data are available (e.g., lung, liver, bone, or bone marrow). 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.
    - **lower energy photons -** The RAC concurs that an RBE in the range of 2 to 2.5 seems reasonable for low-energy photons and electrons for purposes of setting radiation protection standards
    - **beta particles** – The RAC concurs that an RBE in the range of 2 to 2.5 is reasonable for estimating the cancer risk from exposure to tritium.
- **additional uncertainty –**An additional source of uncertainty in risk estimates is associated with the mechanistic biophysical model that is used in BEIR VII to support the LNT model in the low dose region. In Appendix A, the RAC provides a brief review of current research and recommends that ORIA remain aware of the research continuously updating the biophysical model used to support the estimates of radiation risk following low dose radiation exposure.

The RAC finds that the EPA is warranted in modifying the BEIR VII methodologies in several specific areas where the EPA's particular application requires some adaptation of the

BEIR VII approach. The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A. population for a standard stationary population, that is a 'fixed cohort' based on death rates for the year 2000 is a reasonable adaptation of the BEIR VII approach. 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.

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 strongly endorses the EPA-ORIA's desire to estimate uncertainty bounds for its radiogenic cancer risk estimates. 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. Other sources of error and/or uncertainty identified by the EPA-ORIA which should be considered include dosimetry, disease detection, disease classification, temporal patterns, and appropriate RBE values.

The RAC considered several additional complications that could influence uncertainty. One such complication arises in the extrapolation, to lower dose ranges, of radiation effects seen in at dose levels for which statistically significant increases in cancer mortality or incidence have been observed in the LSS and other epidemiological studies of exposed populations. At such lower dose ranges, risk estimates are based on an assumed LNT dose-response model and method of extrapolation from higher-dose/higher-response data. This extrapolation may result in the risk estimates associated with doses in the low-dose range having larger relative uncertainties than those in the higher dose range.

It is important to note that there is an opportunity to implicitly include (qualitative) uncertainties in the choice of risk model per se in the overall (quantitative) uncertainty analysis. That is, a major issue with the choice of the LNT model is whether it is appropriately applied at low doses. In the quantitative uncertainty analysis, this qualitative uncertainty in model choice can be included as a quantitative uncertainty in the DDREF value. The RAC thus strongly endorses the EPA-ORIA's intention to include uncertainty in DDREF in the overall uncertainty analysis.

BEIR VII specifically considered adaptive response, genomic instability, and bystander effects, and concluded that currently there is insufficient evidence to explicitly add these effects to the dose-response model. In the absence of compelling scientific evidence to do otherwise,

the RAC endorses the EPA-ORIA's plan to follow BEIR VII and use the LNT model for calculation of radiation risk.

When estimating radiation-induced cancer risks in any human population it is important to recognize that typically the baseline overall cancer incidence and mortality rates are high and variable, representing >40% and about 23% of the 15 leading causes of illness and deaths in the U.S.A. in 2003, respectively (CDC/NCHS National Vital Statistics System, 2003) Baseline cancer rates have been found to be influenced by various environmental factors such as chronic infections, life style, diet and human factors such as genetic background (WHO, Stewart and Kleihues 2003). In addition, the dose of interest to any "radiation exposed" population is in addition to a highly variable natural background radiation dose (lower limit lifespan dose 60 mSv) that changes as a function of elevation, geographical location and human activities. Depending on the study design, epidemiological studies typically match the "exposed" or "diseased" study population to a "non-exposed" or "non-diseased" comparison population with respect to the variables known to influence baseline cancer rates so as to statistically relate the effect of the exposure to the health outcome of interest as precisely as possible. At radiation exposures in the range of natural background, it is difficult to distinguish radiation-induced changes in risk from the baseline. Thus, as a cautionary note, the RAC recommends that the EPA discuss potential problems associated with the use of LNT dose response model risk estimates in very low dose settings. Currently at these low doses, statistically significant differences between the cancer rates among "exposed" (defined study populations) and "non-exposed" (defined comparison populations) are not observed. These near background doses are only a fraction of those that have been found to be associated with statistically significant differences in cancer frequency between "exposed" and "non-disposed" populations.

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

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

In summary, the SAB finds that the draft dated August 1, 2006 and entitled *"Modifying EPA Radiation Risk Models Based on BEIR VII,"* is an important document to provide the basis for EPA's update of radiogenic cancer risk estimates. The RAC appreciates the opportunity to review this draft document and hopes that the recommendations contained herein will enable EPA to implement changes in the methodology for estimating radiogenic cancers and revise the "Blue Book". We look forward to your response to the recommendations contained in this Advisory.

Sincerely,

Dr. M. Granger Morgan	Dr. Jill Lipoti
Chair	Chair, Radiation Advisory Committee
Science Advisory Board	Science Advisory Board

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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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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 Effectivenesss Factor (DDREF) for estimating cancer 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 Relative Biological Effectiveness (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 science of the biological mechanisms underlying cancer induction at low doses of ionizing radiation and of their influence on the biophysical models used to estimate the cancer risk in this dose range. Additional discussion of the biophysical models of radiation effects in the low-dose region is in Appendix A.

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, other solid cancers, and leukemia. 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.

The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A. stationary population, that is a "fixed cohort", based on death rates for the year 2000 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 estimates of risk 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, 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 RBE for medical x-rays is about 2 to 2.5. X-rays are not uniquely different from gamma rays with respect to their biological effects, 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 RBE factor in the range of 2 to 2.5 is reasonable for low-energy photons and electrons for purposes of setting radiation protection standards. The RAC concurs that an RBE factor in the range of 2 to 2.5 is reasonable for tritium.

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 the NMSCs attributable to low to moderate doses of low-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 baseline incidence rates and low mortality due to NMSC, it is inappropriate to include risk estimates for radiogenic NMSC in the estimate of the incidence or mortality risk for radiogenic cancer.

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 ^{90}Sr. The EPA proposes to divide the bone cancer risk observed in humans exposed to alpha particles from ^{224}Ra by an RBE to estimate the bone cancer risk from ^{90}Sr. The RAC concurs with this practical, operational approach to radiation protection.

BEIR VII does not provide risk estimates for *in utero* exposure to radiation, but the EPA requires an estimate for its guidance documents. The RAC concludes that it would be reasonable for the EPA to use the referenced estimates of cancer risk from *in utero* exposure to external radiation sources, and the dose coefficients provided by the ICRP as a basis for developing its risk estimates for *in utero* radiation exposure from internally-deposited radionuclides.

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

The RAC strongly endorses the EPA-ORIA's desire to estimate uncertainty bounds for its radiogenic cancer risk estimates. 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 Life Span Study (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). Other sources of error and/or uncertainty identified by the EPA-ORIA which should be considered include dosimetry, disease detection, disease classification, temporal patterns, and appropriate RBE values.

The RAC considered several additional complications that could influence uncertainty. One such complication arises in the extrapolation, to lower dose ranges, of radiation effects seen in at dose levels for which statistically significant increases in cancer mortality or incidence have been observed in the LSS and other epidemiological studies of exposed populations. At such lower dose ranges, risk estimates are based on an assumed LNT dose-response model and method of extrapolation from higher-dose/higher-response data. This extrapolation may result in

the risk estimates associated with doses in the low-dose range having larger relative uncertainties than those in the higher dose range.

BEIR VII specifically considered adaptive response, genomic instability, and bystander effects, and concluded that currently there is insufficient evidence to explicitly add these effects to the dose-response model. The EPA-ORIA proposes at the present time to follow BEIR VII and use the LNT model combined with a DDREF for calculation of radiation risk. In the absence of compelling scientific evidence to do otherwise, the RAC endorses the EPA-ORIA's plan in this regard.

When estimating radiation-induced cancer risks in any human population it is important to recognize that typically the baseline overall cancer incidence and mortality rates are high and variable, representing >40% and about 23% of the 15 leading causes of illness and deaths in the U.S.A. in 2003, respectively (CDC/NCHS National Vital Statistics System, 2003) Baseline cancer rates have been found to be influenced by various environmental factors such as chronic infections, life style, diet and human factors such as genetic background (WHO, Stewart and Kleihues 2003). In addition, the dose of interest to any "radiation exposed" population is in addition to a highly variable natural background radiation dose (lower limit lifespan dose 60 mSv) that changes as a function of elevation, geographical location and human activities. Depending on the study design, epidemiological studies typically match the "exposed" or "diseased" study population to a "non-exposed" or "non-diseased" comparison population with respect to the variables known to influence baseline cancer rates so as to statistically relate the effect of the exposure to the health outcome of interest as precisely as possible. At radiation exposures in the range of natural background, it is difficult to distinguish radiation-induced changes in risk from the baseline. Thus, as a cautionary note, the RAC recommends that the EPA discuss potential problems associated with the use of LNT dose response model risk estimates in very low dose settings. Currently at these low doses, statistically significant differences between the cancer rates among "exposed" (defined study populations) and "non-exposed" (defined comparison populations) are not observed. These near background doses are only a fraction of those that have been found to be associated with statistically significant differences in cancer frequency between "exposed" and "non-disposed" populations.

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

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

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

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

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. EPA's ORIA requested the SAB to review the Agency's draft White Paper and provide advice regarding the proposed approach to dose-response assessment of radionuclides.

2.2 Review Process and Acknowledgement

In response to ORIA's request, the SAB 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).

There are various levels of reviews which EPA can request from the SAB. These include reviews, advisories, and commentaries. The request from EPA-ORIA was for an "advisory" review of the draft White Paper. ORIA was interested in vetting ideas with a group of scientific experts on how to incorporate the changes in cancer risk models described by BEIR VII and to extend the BEIR VII models to areas not specifically addressed by the BEIR VII committee. ORIA described it as a "mid-course correction" which would allow the RAC to provide advice

on a series of questions which would guide the Agency in incorporating the latest scientific thinking into their risk estimates. The RAC was not asked to provide policy direction, therefore the RAC did not consider the implications to EPA standards which may be an outcome of the changes to the risk estimates.

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. These notices, the charge to the RAC and other supplemental information may be found at the SAB's Web site (http://www.sab.gov/sab). The quality review draft advisory dated July 18, 2007 was forwarded to the Chartered SAB on (insert date). This advisory reflects the suggested editorial changes from the Charter Board (see 72 Fed. Reg _____, dated and add new reference to **FR** for Charter Board's quality review to references cited section).

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

2.3 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.

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

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

2.5 EPA's Proposed Adjustments and Extensions to BEIR VII Models

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

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

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

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

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

<u>Uncertainty Estimates</u>

BEIR VII provides quantitative uncertainty bounds for each of its risk coefficients, however, no uncertainty was assigned to the form of the dose-response relationship. It was implicitly assumed that the dose-response relationship followed the hypothetical dose-response curve depicted in its Figure 10-1. This shows a progression of linear approximations, with different slopes within different dose ranges. The relationship between these different slopes provides the definition of the DDREF. This progression allowed the BEIR VII Committee to place uncertainty on bounds of the DDREF. Mechanisms pertaining to the biological effects of low-level ionizing radiation are being investigated. This could eventually mandate a different dose-response model, potentially resulting in changes in estimates of risk at low doses. Assigning probabilities to alternative models would be highly subjective at this time. The EPA does not propose to quantify the uncertainty pertaining to low-dose extrapolation, but it would provide a brief discussion of the issue.

2.6 EPA Charge to the Committee

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.

2) In addition to the overall approach described in BEIR VII, the draft White Paper presents specific modifications and extensions. Please comment on the soundness of the following proposals:

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

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

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

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

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

f. 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).

g. 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).

h. 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.

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.).

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?

3. RAC's PHILOSOPHY OF APPROACH FOR RESPONSE TO THE CHARGE

In providing advice in response to the Agencys's specific request, 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. In this Advisory, the RAC wishes to comment on both issues.

For the purposes of providing estimates of the risks of radiation-induced cancers as a basis for setting radiation protection standards, 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 use of an LNT model combined with the DDREF for estimating risks following low dose exposures. By "low dose," the RAC follows BEIR VII's definition; that is, doses below 100 mSv (0.1 Sv), in the context of low-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.

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. As BEIR VII acknowledges, the epidemiological data below 100 mSv (0.1 Sv) are not sufficient by themselves for risk estimation, and considerable cellular and animal data suggest complexities beyond the application of a simplified DNA damage model which historically has been used as support for an LNT dose-response model. The RAC also wishes to emphasize 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 science of the biological mechanisms underlying cancer induction at low doses of ionizing radiation and of their influence on the biophysical models used to estimate the cancer risk in this dose range. Additional discussion of the biophysical models of radiation effects in the low-dose region is in Appendix A.

4. RESPONSE TO CHARGE QUESTION 1: APPLICATION OF THE OVERALL APPROACH AS DESCRIBED IN THE DRAFT WHITE PAPER

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 to remove the variability in risk estimates associated with differences in cancer rates in age and race distributions across locations and calendar years in the U.S.A. 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.

5. RESPONSE TO CHARGE QUESTION 2: WHITE PAPER MODIFICATIONS AND EXTENSIONS

5.1 Charge Question # 2

In addition to the overall approach described in BEIR VII, the draft White Paper presents specific modifications and extensions. Please comment on the soundness of the following proposals:

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

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

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

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

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

f. *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).*

g. *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).*

h. *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.*

5.2 Response to Charge Question # 2a

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

The RAC agrees that the proposed estimation of radiogenic cancer risks for the U.S.A. population using a standard stationary population based on the year 2000 death rate, or fixed cohort is a reasonable adaptation of the BEIR VII approach. Specifically, the use of a stationary population produces risk estimates standardized to a population with fixed age and race distributions. This approach removes the variability in risk estimates associated with differences in cancer rates in age and race distributions across locations and calendar years in the U.S.A. population. This approach is also consistent with the EPA's established approach to cancer risk estimation from exposures to chemicals (U.S. EPA. 2005a, U.S. EPA. 2005b, Also **FR** Vol 70, No. 66, pp 17765, April 7, 2005)

5.3 Response to Charge Question #2b

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

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.

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

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

5.4 Response to Charge Question #2c

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

The RAC notes that there is considerable uncertainty in the application of risk estimates developed from the Japanese atomic bomb survivors to the U.S.A. population. This uncertainty results from different genetic and lifestyle characteristics of the two populations and differences in the baseline cancer risks. 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 is consistent with the method used previously by the EPA in FGR-13. The RAC notes that the EPA method has the advantage of allowing the risk results from multiple exposures to be integrated, thereby enabling the risk from chronic lifetime exposure to be calculated.

5.5 Response to Charge Question #2d

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

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

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

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

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

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

Table 1: Comparison of the EPA White Paper (WP) and BEIR VII Method for Combining EAR and ERR LAR Projections for Lung Cancer Incidence.[1]

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

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

[1]Results are shown for stationary populations and SEER incidence data for the years 1998-2002.
[2]Weight for projection based on EPA proposal
[3] Weight for projection using BEIR VII.

● Consider how the additive ERR model for smoking and radiation provides evidence for the appropriate weighting scheme.

● Consider papers additional to Pierce (2003) on the nature of the smoking /radiation interaction.

Based upon EPA's response to these requests, Table 1 illustrates the effect upon LAR estimates for lung cancer incidence of several different weighting schemes for the EAR and ERR risk models. The columns labeled White Paper (WP) and BEIR VII reflect differences in how the weighting was applied. BEIR VII used a weighted average of the final age-adjusted ERR and EAR estimates on a log scale, while EPA first weighted each age-specific stratum and then combined the weighted age-specific risk estimates. Inspection of the table reveals that the difference in application of the weights produced very small changes in the WP and BEIR VII LAR estimates. The weighting of 0.0 for ERR proposed by EPA produces LAR estimates that are somewhat smaller than the weight of 0.3 for ERR chosen by BEIR VII, most notably for females. The RAC also notes that the evidence for a purely additive model is not compelling

based upon the literature review performed by EPA. There is some support for an interaction between radiation exposure and cigarette smoking that is intermediate between additive and multiplicative, similar to the weighting scheme selected by BEIR VII.

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

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 the approach used by BEIR VII to estimate the risk of breast cancer in females, and that this approach differs from that used by BEIR VII to estimate the risks for the majority of other solid cancers. However, the EPA questions some aspects of BEIR VII's breast cancer risk estimation method, in particular the changing clinical course of breast cancer in conjunction with the relatively long survival period. Thus, the EPA 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 those based on the Japanese atomic bomb survivors, is that they involved a very brief, whole-body exposure to radiation from an external source. In such a situation, all of the organs and tissues of the body were irradiated and the long-term risks to these organs and tissues have been studied directly. When dealing with internally deposited radionuclides, the situation is different because the radionuclide is likely to be distributed non-uniformly in the body, with only a few organs and tissues receiving most of the dose. This can change the spectrum of cancers produced. Also, because of the possible long-term retention of some long-lived radionuclides, the dose can continue to accumulate at a low dose rate over months or years. Dealing with these differences is important but not necessarily straightforward as discussed below.

Higher LET Radiation

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

Alpha Particles

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

<u>a) Data from human populations exposed to alpha-emitting radionuclides.</u>

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

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

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

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

Sizeable data bases are available for different species of laboratory animals exposed via various routes to graded activity levels of different beta-, gamma- or alpha-emitting radionuclides and studied for their lifetimes. These studies provide much information on the life-span health effects but the number of variables involved including species, route of exposure, animal husbandry and other factors make it difficult to extrapolate the risk results directly to human populations in a consistent manner. However, they do provide useful information on radionuclides for which no human data are available. Such studies also help define the influence of dose distribution and the relative effectiveness of high- and low-LET radiations in those cases where studies of the high and low-LET emissions were examined in a parallel manner under similar conditions.

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

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

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

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

The RAC recognizes the problems that the EPA has to deal with in adding consideration of alpha-emitting radionuclides to the information already provided for low-LET radiation in the BEIR VII report. This particular issue is one example of the need for a practical, operational public health approach to radiation protection and standards setting mentioned earlier in this Advisory. On this basis, the RAC is supportive of the use of a generally accepted RBE_M value such as the 20 that they are using currently. For those radionuclides for which human cancer risk data are available for the 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 (except for bone cancer as discussed in Section 5.8) of using the low-LET cancer risk from BEIR VII multiplied by RBE_M.

Low-energy Photons and Electrons

The EPA White Paper suggests that the relative biological effectiveness (RBE) for medical x rays is about 2 – 2.5. However, x-rays are not uniquely different from gamma-rays

except for their production. Any risk estimate associated with exposure to photons needs to be correlated with the energy of the photon rather than the method of production.

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

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 ^{90}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 ^{224}Ra by an RBE to estimate the bone cancer risk from ^{90}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 low-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 baseline 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.

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

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

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

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

Given the paucity of the epidemiological data available for estimating cancer risks of *in utero* exposure to low or high LET, RAC advises that ORIA continue to monitor advances in the subject area, as well as the science of the biological mechanisms underlying cancer induction in such situations and of their influence on the biophysical models used to estimate the cancer risk of *in utero* exposure.

The RAC concludes therefore that it would be reasonable for the EPA to use the cancer risk estimates from the published studies of populations exposed to photons *in utero* as a basis for developing its estimates of cancer risk for such exposures. The RAC similarly advises EPA to use the dose coefficients provided by ICRP as a basis for developing its estimates for *in utero* radiation exposure from internally-deposited radionuclides.

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). Under-estimation and over-estimation of risk potentially lead to under- and over-regulation, respectively, each of which have costs associated with them. 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 this the RAC suggests that the EPA-ORIA should consider performing a quantitative analysis of uncertainty in the components of the risk assessment equations to establish uncertainty in the final estimate of risk. This process should be expanded to include a sensitivity analysis that establishes a ranking of the input parameters. This ranking can provide a valuable tool for determining which components merit further consideration, with the possible acquisition of additional data, and those that do not merit further consideration because the influence of these uncertainties on the final result is small.

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

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

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

It is important to note that there is an opportunity to implicitly include (qualitative) uncertainties in the choice of risk model per se in the overall (quantitative) uncertainty analysis. That is, a major issue with the choice of the LNT model is whether it is appropriately applied at low doses. In the quantitative uncertainty analysis, this qualitative uncertainty in model choice can be included as a quantitative uncertainty in the DDREF value. The RAC thus endorses the Agency's intention to include uncertainty in DDREF in the overall uncertainty analysis.

There is also a need to evaluate uncertainty following exposure to high doses delivered at low dose-rates. In addition to the DDREF, it may be necessary to have a dose rate effectiveness factor (DREF). The major data sets for these types of exposure come from internally deposited radioactive materials both in experimental animals and in humans where the dose rates can be low, but the total lifetime dose can be very high. The prime examples of such exposures in humans are the doses to the lungs of uranium miners from inhaled radon/radon daughters inhaled by uranium miners (1) (U.S. NAS/NRC. 1999. BEIR VI, page 67) and the dose to bone from internally deposited radium in the radium dial painters (2) (Roland 1994).

In the uranium miners, there was an "inverse dose rate effect" when miners were exposed to high total doses (WLM Working Level Months) over a relatively short time period (months to a few years). These miners show a lower risk that seen in miners with the same total dose or

WLM given over many years. However, it was determined that the mechanism of action for high and low dose rate exposures were different and that "…the inverse exposure-rate effect found in the miner data should not modify the risks for typical indoor exposures." (BEIR VI, page 9).

The bone cancer frequency in the radium dial painters remained essentially at zero until the total bone dose from the internally deposited alpha emitting radionuclide reached about 10 Gy, after which it increased rather markedly. This has been used to suggest a threshold dose below which bone sarcomas are not induced by radiation exposure. Similar data were seen in dogs that were exposed to beta emitting ^{90}Sr-^{90}Y by either inhalation (3) (Gillett et al. 1992) or ingestion (4) (White et al. 1993). These low dose-rate exposures caused non-detectable changes in cancer risk or life shortening until the total dose became very high (5) (Raabe et al. 1981).

This discussion illustrates that the cancer risk estimates derived for acute exposure, even with a DDREF of 1.5-2.0, do not result in accurate prediction of cancer risk to populations exposed to high doses delivered at low dose rates. Such information needs to be considered when predicting long term risk from low dose-rate exposures.

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

7. RESPONSE TO CHARGE QUESTION 4: ISSUES RELATING TO RADIOGENIC THRYOID CANCER NOT QUANTIFIED IN BEIR VII AND ISSUES BEYOND THE CHARGE

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.

8. ISSUES BEYOND THE CHARGE

The RAC received written and oral comments from members of the public which raised concern about the need to set radiation protection standards for the most sensitive population for specific cancer end points, instead of the use of "Reference Man." The RAC understands that in the existing Federal Guidance Report 13, EPA-ORIA has already used the current ICRP age groups (infant, 5-10, 15-20 year olds) in both the cancer risk coefficients and the underlying radiation dose coefficient. The RAC recommends that EPA continue this practice so that individuals using the Federal Guidance for assessing compliance can be explicit about ages and make appropriate assumptions.

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

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

The uncertainty associated with the use of the epidemiological data to estimate risk in the low dose range has been covered in detail in Charge Question 3: Uncertainties not Quantified in BEIR VII. An additional source of uncertainty in risk estimates is associated with the DDREF and the mechanistic biophysical model that is used in BEIR VII to support the LNT in the low dose region. It is well established that it is not possible to use a linear extrapolation from health effects produced by high radiation doses to predict those induced in the low dose and dose-rate region. To make this low dose estimate, the slope of the dose-response relationship in the high dose region is modified by the (DDREF) which corrects for the decreased biological effectiveness of low dose and dose-rate exposures. The resulting lower slope is then linearly extrapolated into the very low dose and dose-rate region below where useful epidemiological data is obtainable. The major question discussed in this appendix is the applicability of the LNT model in this very low dose region.

Although the BEIR VII committee conducted an extensive review of the cell and molecular literature relative to biological responses at low doses and discussed the recent advances, they concluded that the mechanistic cell and molecular biological research supported the current biophysical model that they use (US NAS/NRC. 2006. BEIR VII, pp. 63-64). However, the rapid increase in information on the biological responses to low doses of radiation suggest new paradigms in radiation biology (Brooks 2005) that may modify the biophysical model used in the BEIR VII report.

BEIR VII uses a biophysical model that suggests that each and every ionization increases the probability of a DNA breakage (Burma et al. 2001) and that this results in a linear increase in the risk for mutations and therefore in the risk for cancer (US NAS/NRC. 2006. BEIR VII, pp. 10-11). This model assumes independent action of cells and a lack of cell communication. The model suggests that there is no change in response as a function of previous radiation exposure and that there is a linear link between unrepaired DNA damage, rare mutational events and the development of cancer. Recent research has been conducted to provide a solid data base on the response of molecules, cells, tissues and organisms to very low doses and dose rates of radiation (Ko et al. 2004.; Azzam and Little 2004.; Little 2006.; Brooks 2005.; Mitchel et al. 2004.). This research has suggested that several of the assumptions used in the BEIR VII biophysical model may no longer be valid (Tubiana 2005). The data base that questions the assumptions used by

BEIR VII include information on dose dependent changes in gene expression, radiation induced changes in redox status of the cells, apoptosis, bystander effects, adaptive responses, and genomic instability (Spitz et al. 2004; Di Masi et al. 2006.; Coleman et al. 2005.; Azzam and Little 2004.; Little 2006.; Brooks 2004.). The BEIR VII report has discussed each of these effects and concluded that until molecular mechanisms of action involved in the induction of low dose biological effects are elucidated, they cannot be utilized in modification of dose-response relationships. This appendix provides a brief review on the mechanistic research being conducted and to suggest the need for continuously updating the biophysical model used to support the estimates of radiation risk following low dose radiation exposure.

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

Genomic instability suggests that, in addition to rare mutational events, frequent radiation-induced changes following exposure may play an important role in cancer induction. Radiation-induced genomic instability is seen at a high frequency in cells many cell divisions after the radiation exposure (Morgan 2003; Ponnaiya et al. 1997.). The instability results in increased frequency of mutations, chromosome aberrations, and cell killing. Radiation-induced genomic instability seems to be one of the early stages in the carcinogenesis process and has been seen both *in vitro* and *in vivo*. These observations challenge the relative importance that initial mutations play in radiation-induced cancer (Kadhim et al. 2004.). The BEIR VII biophysical model suggests that since DNA damage increases as a linear function of acute radiation dose that there must be a linear increase in cancer risk (BEIR VII pp. 245). Genomic instability and the ability to modify responses after the radiation exposure both challenge the linear relationship between initial DNA damage and cancer frequency.

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

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

APPENDIX B –ACRONYMS

A-Bomb	Atomic Bomb
AM	Arithmetic Mean
AR	Absolute Risk
BCC	Basal Cell Carcinoma
BEIR	Biological Effects of Ionizing Radiation
BEIR VII	*Health Risks from Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2*
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Co	Chemical symbol for cobalt (^{60}Co isotope)
DDREF	Dose and Dose-Rate Effectiveness Factor
DFO	Designated Federal Officer
DNA	Deoxyribonucleic Acid
EAR	Excess Absolute Risk
EPA	Environmental Protection Agency (U.S. EPA)
ERR	Excess Relative Risk
FR	Federal Register
FGR-13	Federal Guidance Report 13
GM	Geometric Mean
GMC	Geometric Mean Coefficient
GSD	Geometric Standard Deviation
Gy	gray, SI unit of radiation absorbed dose (1Gy is equivalent to 100 rad in traditional units)
H	Chemical symbol for Hydrogen (^{3}H isotope)
I	Chemical symbol for Iodine (^{131}I isotope)
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements, Inc.
IREP	Interactive RadioEpidemiological Program
keV	kiloelectron Volts
LAR	Lifetime Attributible Risk
LET	Linear Energy Transfer
LNT	Linear Non Threshold
LSS	Life Span Study
mSv	milli-Sievert
NAS	National Academy of Sciences (U.S. NAS)
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NMSC	Non-Melanoma Skin Cancer
NRC	National Research Council
OAR	Office of Air and Radiation (U.S. EPA/OAR)
ORIA	Office of Radiation and Indoor Air (U.S. EPA/OAR/ORIA)

PAG	Protective Action Guide
Pu	Chemical symbol for Plutonium (^{239}Pu Isotope)
QA	Quality Assurance
QC	Quality Control
QA/QC	Quality Assurance/Quality Control
R	roentgen
Ra	Chemical symbol for Radium (Isotopes include ^{224}Ra, ^{226}Ra, ^{228}Ra, and ^{236}Ra)
RAC	Radiation Advisory Committee (U.S. EPA/SAB/RAC)
rad	Traditional unit of radiation absorbed dose in tissue (a dose of 100 rad is equivalent to 1 gray (Gy) in SI units)
RBE	Relative Biological Effectiveness
RBE_m	Maximum Relative Biological Effectiveness
REF	Radiation Effectiveness Factor
rem	Radiation equivalent in man; traditional unit of effective dose equivalent (equals rad x tissue weighting factor) (100 rem is equivalent to 1 Sievert (Sv))
RERF	Radiation Effects Research Foundation
R/h	Roentgen per hour; traditional measure of exposure rate
Rn	Chemical symbol for Radon (^{222}Rn Isotope)
RR	Relative Risk
SAB	Science Advisory Board (U.S. EPA/SAB)
SCC	Squamous Cell Carcinoma
SEER	Surveillance, Epidemiology, and End Results
SI	International System of Units (from NIST, as defined by the General Conference of Weights & Measures in 1960)
Sr	Chemical Symbol for Strontium (^{90}Sr Isotope)
Sv	sievert, SI unit of effective dose equivalent in man (1 Sv is equivalent to 100 rem in traditional units)
Th	Thorotrast (^{232}Th Isotope)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
US	United States
WLM	Working Level Months

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