RAC Subgroup A Draft – 3/25/09

Weighting of ERR and EAR rates/risks in the computation of lifetime risk estimates (Item 1b)

The committee was asked to review EPA's weighted geometric mean approach for combining the ERR and EAR based risk estimates when transporting the risk models developed largely from data on Japanese atomic bomb survivors to a US population. The site-specific risk estimates in BEIR VII were computed as a weighted geometric mean of ERR- and EAR-based lifetime absolute risk (LAR) estimates for the current (2000) US population. EPA has proposed a method in which they compute an average excess risk function as a weighted geometric mean of age-(and age-at exposure) specific excess rates for the ERR and EAR models and then apply this average excess rate function to a stationary US population to compute the LAR. EPA was specifically interested in the committee's views on the decision to use an average excess rate function rather than averaging the ERR- and EAR-based LAR estimates. During our meeting with the EPA staff it was explained that their primary motivation for development of their average rate method was to insure additivity of the age-specific risks.

The committee felt that the question of whether to use weighted geometric or arithmetic means to combine the ERR and EAR risk estimates was more important than the question of whether to average excess rates and compute the LAR or to average LAR estimates. We recommend that the LAR computations make use of the arithmetic mean even though this is a departure from the BEIR VII approach. The primary reason for this recommendation is that the geometric mean implicitly gives more weight to the lower risk estimate whereas when risks (or excess rates) are averaged using weighted arithmetic mean the choice of weights explicitly captures judgments about the relative importance of the ERR-and EAR-based risk estimates. Furthermore, the use of arithmetic means to combine the risk estimates insures additivity of the age-specific risk estimates. Therefore, we recommend that the report should present both ERR-and EAR-based LAR estimates and then compute, as in BEIR VII, their suggested risk estimate as a weighted arithmetic mean of the two estimates. The report should present both the ERR- and EAR-based estimates together with the recommended ERR-weight together with the weighted LAR estimates

In our discussions we recognized that our proposal differs from the BEIR VII approach. Dr. Gilbert, who was a member of the BEIR VII committee and played a central role in the development of their risk estimates, indicated that there was no serious discussion of how best to combine ERR- and EAR-based risk estimates and that geometric means were used primarily because they simplified the largely analytical uncertainty assessment carried out for BEIR VII. EPA is using a Bayesian monte-carlo method to evaluate the uncertainty in which the form of the nature of the computations is independent of the

way in which risks are averaged. Furthermore, the risk estimates presented in the recent ICRP recommendations and the UNSCEAR 2006 report used weighted arithmetic means to combine the ERR- and EAR-based risk estimates.

One question that arises if weighted arithmetic means are used in place of weighted geometric means is whether EPA should change the ERR/EAR weights recommended by BEIR VII. We do not believe that this is necessary since it is almost certainly the case that in choosing these weights the BEIR VII members were thinking in terms of linear (arithmetic) weights. However, we do recommend that the report include some discussion of why, in most cases, greater weight is given to the ERR-based risks than to the EAR-based risks and why this is not done in some cases (primarily breast cancer).

The RAC feels that the decision to use a stationary population rather than a census based population is in the LAR computations is reasonable. The reasons for this change were made cogently described in the EPA staff presentation to the RAC. The report should be revised to include additional material on the reasons for use of a stationary population. It might also be useful to include some indication how the stationary population differs from the BEIR VII census based population (e.g., presentation of a gender-specific population pyramids or age-adjusted rates for selected cancers) and, perhaps only for solid cancers as a group, how the switch from a census based population to a stationary population affects the risk estimates.

Computation of risks for breast cancer mortality (Item 1d)

BEIR VII mortality risk estimates were computed scaling age-specific incidence risks by the ratio of the (age-specific) mortality-to-incidence rate ratios. EPA has proposed replacing this simple ratio by a factor that allows for the relative survival of breast cancer patients. The data presented to the RAC by EPA-staff strongly suggest that modified method leads to more realistic breast cancer mortality risk estimates. The augmented RAC believes that EPA's method is an improvement over the BEIR VII methods since the relative survival of breast cancer patients is quite high and since the ERR and EAR risk estimates used in the LAR computations change (decrease) with increasing attained age. EPA should consider using a similar approach in computing mortality risks for other types of cancer, particularly those with relatively relative survival rates.

Other issues (Item 3a-c)

Material on non-cancer mortality

The current report focuses on cancer mortality and incidence, and does not address the possibility of radiation-related non-cancer mortality. Non-cancer mortality, particularly mortality from cardiovascular disease, has been linked with exposure to high therapeutic radiation doses (BEIR VII), but it is not clear whether such effects are found at lower doses. Mortality from most broad non-cancer disease categories has been found to be related radiation dose in the LSS cohort (ref.). However, because the

identified radiation risks were small compared to baseline risks, it was not possible to evaluate age effects or the shape of the dose-response function with any precision. For example, it was not possible to distinguish a linear dose-response from a dose-response with a threshold as high as 0.5 Gy. Because of these uncertainties, lifetime risk estimates could range from zero to levels that approach those for cancer mortality estimates. Due to the uncertainties in quantifying risks and uncertainty in whether or not there is any risk at low doses, the decision of EPA not to provide lifetime risk estimates for non-cancer mortality is reasonable. However, we recommend that non-cancer mortality be mentioned as a possible effect of radiation exposure even at low doses, and that the reasons for not providing risk estimates for this endpoint at the present time be stated.

ICRP and UNSCEAR reports

Since the publication of BEIR VII, both ICRP (ref) and UNSCEAR (ref) have published reports that include lifetime risk estimates for radiation-related cancers. ICRP developed estimates for a world population, whereas UNSCEAR developed estimates for several different countries, including the United States. We recommend that the EPA add a brief description of the methods used in the ICRP and UNSCEAR reports and discussion of how they compare with those that are being used by EPA. Tables showing comparisons of EPA estimates with relevant estimates from ICRP and from UNSCEAR would also be a desirable addition to the report.

Additional points

- Some of the more detailed explanations and examples provided in the materials orally presented on March 23, 2009 should be reviewed for inclusion in the Blue Book as appropriate.
- Additional information on the updated SEER data (e.g., use of SEER Stat) would be helpful. We feel that the statement on page 55 that increased LAR estimates (compared to those of FGR 13) are "largely attributable to the use of more recent SEER incidence [rates]" is somewhat confusing. The main point seems to be that FGR 13 made use of (poorly) approximated incidence rates computed as lethality-adjusted mortality risks but the new estimates are based on actual age-specific incidence rates.
- We believe that the switch to arithmetic means and averaging LAR's in place of averaging excess rates should improve the consistency between the suggested risk estimates and the central (mean/median) estimates from the uncertainty analysis. However, the report should include an enhanced discussion / explanation of the uncertainty distribution was not the basis for the central estimates.
- A general discussion regarding the impact of sources of error not considered in the development of the uncertainty distributions is needed for transparency. For example, in regard to the transfer of risk between the LSS cohort and the U.S., a discussion of the potential impact on the uncertainty distribution if the true transfer model falls outside the limits defined by the purely additive and purely multiplicative risk transfer is needed.
- Tables with LAR estimates should clearly indicate whether or not the estimates included a DDREF adjustment.

- There should be more discussion of issues related to lympho-hematopoietic cancers including (for example: a) comments on the recent literature suggesting that CLL may be a radiogenic cancer (e.g., Linet et al. 2007 and appropriate references contained within); b) the reasons for not developing risk estimates for leukemia subtypes; and c) why risk estimates have not been presented for (non-hodgkins) lymphoma or multiple myeloma.

  Linet MS, Schubauer-Berigan MK, Weisenburger DD, Richardson DB, Landgren O, Blair A, Silver S, Field RW, Caldwel G, Hatch M, Dores GM. Chronic Lymphocytic Leukemia: An Overview of Etiology in Light of Recent Developments in Classification and Pathogenesis, *British Journal of Haematology*, 139, 672-686, 2007.

Other ideas

- Make data (model parameters, stationary parameters, smoothed survival functions, etc) and basic estimation programs available.
- Include additional descriptive information on uncertainty distributions, e.g. means and some percentiles for adjustment factors
- More clearly define what is meant by uncertainty factor

Question #1. a. Approaches for extending risk estimates to radiations of different LETs – in particular, deriving site-specific risk estimates for alpha or low-energy electron and photon radiations based on models derived from the A-bomb survivors, who were primarily exposed to higher energy gamma rays (see Section 5).

Low-Energy Electron and Photon Radiations

There was considerable discussion regarding proposed changes to the RBE for low energy β particles and photons. This discussion focused on:

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

In their previous comments on the white paper, RAC supported EPAs use of an effectiveness factor of 2 – 2.5 for photons less than 30 keV and tritium β particles. In light of the current discussion RAC now suggests that EPA provide a detailed argument/justification to support such a change to the RBE. It's RAC's understanding that EPA plans to prepare a paper for peer review publication on this topic that will address these issues. Similar, more detailed justifications are recommended for changes to the RBE for medical x-rays (to ~ 1.4). Given that medical radiation exposure(s) make up the majority of the average US individuals radiation exposure, the implications for individuals undergoing medical exposures to mammograms or CT scans in the long term might well be significant.

This is particularly important in light of the paragraph on Blue Book page 95. "Risk coefficients derived from studies of cohorts medically irradiated with x rays are in some cases lower than what has been observed for the A-bomb survivors."

Alpha Radiation

The general approach for alpha emitters using risk estimators from specific epidemiological studies when reliable estimates are available is acceptable and using an RBE of 20 when reliable estimates are not available also appears to be a reasonable approach. The choice of estimators for each specific cancer site are discussed below.

DRAFT

Question #1. c. and e. Estimation of risks not specified in BEIR VII, including kidney, bone, and skin cancers, as well as for alpha particle irradiation of the liver (see Sections 3.3 and 5.1) and Approach for separating out nonfatal skin cancers and risks from prenatal exposures from the overall risk estimates (see Sections 3.3 and 6).

Kidney:

Recently the IOM reviewed the literature on the effects of potential uranium exposures as part of their analysis of depleted uranium health effects. The Committee concluded that there was no evidence of kidney cancer resulting from uranium exposures. This involved a wide variety of studies, both occupational and environmental. Animal studies did not provide evidence of kidney cancer after uranium exposures.

Bone:

The RAC notes that the Advisory on the Agency Draft White Paper published in 2008 (section 5.7, p. 19) supported the use of the human data to derive estimates of the bone cancer risk from 224 Ra. The use of that data from the study of radium dial painters who were exposed to 226Ra and 228Ra was recommended to derive the bone cancer risk of these radionuclides. This recommendation is reiterated as the nature of the exposure (chronic, lifetime) and their biokinetics is different than those of 224Ra.

Skin (Fatal and nonfatal cancers):

EPA responded well to the RAC recommendations. Clarification should be made defining BCC as the only radiogenic cancer.

Liver:

As a target organ for certain alpha particle emitters including colloidal Thorotrast and plutonium, the liver is at risk for radiogenic cancer in exposed individuals. Comparison of the liver cancer risk estimate for gamma radiation derived from by BEIR VII from the LSS data with that obtained from the follow-up study of Danish Thorotrast patients, suggested an RBE of 20. While recognizing the uncertainties inherent in both studies with respect to liver cancer and this RBE, EPA initially proposed the use of this value (20) with the BEIR VII liver cancer risk estimate to derive
an estimate for alpha particle-induced liver cancer (Draft White Paper, 2006). RAC supported this approach for liver and certain other cancers that have been associated with alpha particle radiation (RAC Advisory, 2008) with the recommendation that any additional epidemiological data be taken into consideration based on additional data from the follow-up study of German Thorotrast patients and a reanalysis of the Danish patient data using an empirical model with a lifetime risk projection, EPA has revised its proposal to use a scaled version of the BEIR VII model whereby BEIR VII's low-LET age and gender- specific liver cancer risk estimates and an RBE of 40 will be used to

provide risk estimates for alpha-particle induced liver cancer at environmental low doses.

This approach seems reasonable, the use of an RBE of 40 seems a reasonable conservative approach. EPA may wish to consider the types of liver cancers for example are the LLS and Thorotrast cancers the same type?

Prenatal:

The estimation of cancer risks from prenatal radiation appears to be appropriately treated in the Draft Report based on the existing literature. Prenatal radiation exposure has been shown in some studies to cause increases in childhood cancers and in the LSS increases in adult cancers.

The Draft Report adopts a childhood cancer risk value of 0.06/Gy for prenatal exposure which was suggested by Doll and Wakeford (1997) and adopted by the ICRP (2000). This value has been controversial because other studies have been equivocal (Boice and Miller 1999), but the value appears to be reasonable based on the reviews of the evidence. This evidence is based upon medical x-rays 80kVp and the risk coefficient would be adjusted to 0.04/Gy if the RBE of 1.4 for medical x-rays is adopted.

The Draft Report recommends for adult cancers from *in utero* exposure adopting the cancer risk models in Section 3 with age set to 0. This recommendation is based on an analysis of A-bomb survivors exposed *in utero* that found a lower risk than those who were irradiated as young children, but the difference is not statistically significant (Preston, 2008). The committee feels that this is a reasonable approach. However some caution must be expressed since there may have been some spontaneous abortions for women who received the higher doses in the periods immediately after the A-bombs that were missed that would lower the estimates of the risks. This should be mentioned in the Report as an additional source of uncertainty for prenatal exposure..

Question #3:

3b) The RAC recommends that a column listing references for the source of the distribution parameters be added to Table 4-2 on sources of uncertainty.

3c) The intended purpose of the document needs to be clearly stated right up front. Also, how this document will be used needs to be clearly stated. More background, clarification would be helpful in aiding understanding. Some pieces are scattered throughout document/hard to put together.

DRAFT

Regarding the issue of balance in the draft blue book in presenting, the negligible discussion and attention to risk estimates arising from the many international studies of nuclear workers is noted. The EPA has stated that the agency's primary concern is with the health effects of low-level, protracted radiation exposure. The EPA also acknowledges that the transfer of risk from an acute, high-level exposure in an Asian population to the U.S. population is problematic. The RAC realizes that the draft blue book is based upon BEIR VII risk estimates using the LSS data, but better balance would be achieved by comparing and discussing differences in risk estimates between the revised EPA estimates and estimates from the 15-country radiation worker study, the study of Mayak workers, and studies of medically irradiated populations. The RAC also notes that the overwhelming majority of these workers received doses less than 100 mGy which is the dose range of interest.

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Overall comments on uncertainty analysis

The methods used for the full uncertainty analysis of stomach, colon, liver, lung, and bladder cancer, are based upon analysis of the data for the Japanese atomic bomb survivors, the Life Span Study (LSS). The entire focus of the uncertainty analysis is upon the calculation of Lifetime Attributable Risk (LAR) per-person Gy for the US population based upon the data for the LSS. The LAR is a complex function of (I) parameters (i.e. risk estimates) estimated statistically using the LSS data, (II) other parameters, e.g, RBE, DDREF, and population transfer, about which little or no direct information comes from the LSS data, and (III) population age distribution in a hypothetical (stationary) population mimicking that of the US population. The goal of the uncertainty analysis in the EPA blue book is to combine sampling variation in parameter estimates for parameters of type (I) with uncertainties in parameters of type (II) to provide an overall uncertainty estimate for the LAR calculated either separately for individual tumor types or for groupings of tumors (e.g. all solid tumors, leukemias, etc). In order to perform this task a Bayesian analysis is provided since this provides a consistent framework for the treatment of unknown parameters as random variables and a formal method for updating initial prior distributions for these random parameters with the information contained in the LSS data about the parameters of type (I). Thus the Bayesian nature of the uncertainty analysis rests upon a somewhat different statistical basis than does the "frequentist" analysis that gives the "best estimates" of LAR for these cancers, and thus it is not surprising that the LAR uncertainty bounds are not completely symmetric around the best estimate. Besides the mere fact that the uncertainty analysis of LAR is Bayesian in nature the Bayesian analysis for stomach, colon, etc., actually is a joint analysis of these cancers and combines information about the linear excess relative risk parameters across these cancer types. It estimates a common mean (but separately by sex) and a common variance in the distribution of these risk parameters. Doing this should have the useful property of reducing the uncertainty in the posterior distribution of these risk estimates especially for rarer cancers where the information in the LSS likelihood is not large.

Because all parameters of type (I) and (II) are regarded as random variables the LAR itself is treated as a random variable (a function of the random variables of type I and II) in the uncertainty analysis.

While this general framework is reasonable it is complicated, especially by the need to provide prior distributions for both the parameters of type (I) and particularly for those of type (II). Since the LSS data has a "lot" of information about survival parameters the prior distributions of type (I) do not very strongly affect the final "posterior" estimates of these parameters, however the prior distributions specified for parameters of type (II) tend to dominate their posterior distributions since there is little or no information about these parameters in the LSS data.

Several important issues about the techniques and the description of the techniques provided by the Blue Book draft were raised by the committee.

DRAFT

First, it should be clearly stated and justified why the Bayesian analysis is not being used as the primary analysis (for providing the "best" estimate) of the LAR. Presumably this is partly because the best estimate of the separate LARs for the specific cancer sites do not impose the constraint that the risk estimates for each cancer be similar; since it not "known" a-priori that such risk estimates should be similar it may be scientifically more sensible to use completely different analyses of each cancer subtype to give the best estimate, even if an assumption of commonality is a reasonable one to impose when evaluating uncertainty especially for relatively rare cancers.

Such an argument should be made by the authors of the Blue Book, however, and moreover this argument would not apply to the LAR when groups of cancers (all cancer or all solid tumors) are analyzed in aggregate. Why not use the fully Bayesian Analysis to provide a best estimate of the LAR for all solid tumors for example?

In general there is an overall lack of clarity concerning the likelihood function for the LSS data. The likelihood function for Poisson regression analysis of grouped survival data may not be very familiar even to relatively statistically knowledgeable readers and should be described carefully. Moreover because for the cancers listed above (stomach, colon, etc.), a joint analysis is being performed (where tables of person years and events are given for more than one outcome) it should be explicitly pointed out that it is legitimate to multiply the likelihoods for each outcome together, even though the same "denominator" values (person years) are being used in each table.

The description of the reasoning leading to the subjective priors shown e.g. in Table 4-1 would also increase the transparency of the manuscript. It would also facilitate future scrutiny and discussion of the elicitation arguments used by the probability assessor.

At present the analyses presented (LAR's and their uncertainty intervals) are not very detailed and give little insight into which of the parameters of type (I) and (II) above are really most influential in "driving" the overall uncertainty analysis of the LAR.

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

Since the uncertainty analyses described in the draft Blue Book use somewhat different models and assumptions than are used in computing the point estimate, the Committee feels that the applicability of the uncertainty ranges to the point estimate should be further investigated. As a means of extending the analysis, we suggest the following. Use the results of the current approach to the uncertainty analysis to identify one (or perhaps two)

DRAFT

key parameters for each point estimate (where 'key' means most contributory to overall uncertainty). Then, in the model used to generate the point estimate, vary the key parameters over their range in a parametric sensitivity analysis (perturbation analysis) to generate a range of resulting risk estimates. This should provide an indication of the operational range of the point estimate. In this way, the results of the current uncertainty analysis can be verified to be appropriate (or not) for the point estimates, and the general width indicated of the confidence intervals for the point estimates.

As a general methodological comment on the usefulness of the posterior densities resulting from a Bayes approach we note that for future risk predictions the concept of the predictive density[1)] should be considered. It is well established in other applications of survival analysis e.g. reliability analysis and takes all remaining parameter uncertainty into account for the calculation of predicted quantities. Increased computing power and advances in numerical integration (e.g. Quasi Monte Carlo Methods) make this feasible if the dimensionality of the integrand is not too high (e.g. < 10). (c.f. Bolstad, Intro to Bayesian Statistics)

Additional comments on risk transfer

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

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

The committee in other sections of this report has indicated a preference for an arithmetic rather than geometric mean-based method of interpolation between the LARs produced by transferring the EAR or the ERR model to the US. A key issue is the weighting of these two models. The general sense of the committee (???) is that weighting probably

DRAFT

should emphasize ERR models more than EAR models. This is based on such general observations that excess relative risk parameters tend to be more similar than excess absolute risk parameters when data from different cancers are considered, or when cancer induction in different laboratory animals is examined. While there certainly are exceptions to this general rule, this seems to provide at least some limited basis for preferring ERR models for transfer between different populations than EAR models. At present there is only a slight bias in favor of ERR models in the methods used by EPA and we suggest placing additional weight on ERR models overall.