Modifying EPA Radiation Risk Models Based on BEIR VII

Draft *White Paper*

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I. Introduction

In 1994, EPA published a report, referred to as the "Blue Book," which lays out EPA's current methodology for quantitatively estimating radiogenic cancer risks (EPA 1994). A follow-on report made minor adjustments to the previous estimates and presented a partial analysis of the uncertainties in the numerical estimates (EPA 1999a). Finally, the Agency published Federal Guidance Report 13 (FGR-13), which utilized the previously published cancer risk models, in conjunction with ICRP dosimetric models and U.S. usage patterns, to obtain cancer risk estimates for over 800 radionuclides, and for several exposure pathways (EPA 1999b).

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

In this paper, we outline proposed changes in EPA's methodology for estimating radiogenic cancers, based on the contents of BEIR VII and some ancillary information. For the most part, we expect to adopt the models and methodology recommended in BEIR VII; however, we believe that certain modifications and expansions are desirable or necessary for EPA's purposes. At this point, EPA is seeking advice from the Agency's Science Advisory Board's Radiation Advisory Committee (RAC) on the application of BEIR VII and on issues relating to these modifications and expansions. After receiving the advisory review, we plan to implement changes in our methodology through the publication of a revised Blue Book, which we would expect to submit to the RAC for final review. The revised Blue Book could then serve as a basis for an updated version of FGR-13.

A. Current EPA Cancer Risk Models

For most cancer sites, radiation risk models are generally derived from epidemiological data from the life span study (LSS) of the atomic bomb survivors. EPA's models for esophagus, stomach, colon, lung, ovary, bladder, leukemia, and "residual" cancers were adapted from the models published by Land and Sinclair based on a linear, no-threshold 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 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 --- "multiplicative" and "NIH "--- differing in how one "transports" risk from the Japanese LSS population to another population, e.g., to the U.S. population. For the multiplicative model, it is assumed that the ERR/Gy is the same in all populations, whereas, for the NIH model, it is assumed that the excess

absolute risk 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, EPA adopted an intermediate "GMC" model for each site, where the ERR coefficients were taken to be the geometric mean of the corresponding ERR coefficients for the multiplicative and NIH models (EPA 1994).

For leukemia, the temporal response in the models was more complex, but the approach for transporting risk to the U.S. population was analogous. Following the approach of Land and Sinclair, EPA also developed a GMC model for kidney from the LSS data. EPA's models for other sites, 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, for low doses and dose rates, each coefficient was reduced by a factor (DDREF) of 2 from what would be obtained from a linear, no-threshold fit to the LSS data.

B. BEIR VII Models

BEIR VII site-specific models derived from the LSS differ from those of Land and Sinclair in several significant ways: (1) they are derived primarily from data on cancer incidence rather than cancer mortality; (2) mathematical fitting is performed to better reflect the functional dependence of solid cancer risk on age at exposure and attained age; (3) a weighted average of risk projection models was used to transport risk from the LSS to the U.S. population; (4) a value for the DDREF of 1.5 was 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 were based on pooled analyses of data from the LSS cohort, together with data on medically irradiated cohorts (Preston et al. 2002, Ron et al. 1995).

C. Proposed EPA Adjustments and Extensions to BEIR VII Models

In implementing its revised methodology for estimating radiogenic cancer risks, EPA proposes to adopt many of the recommendations in BEIR VII. One significant extension to be considered is the estimation of risks from exposures to higher LET radiations, especially to alpha particles, but also to lower energy photons and beta particles. Particularly important in this regard is the risk from alpha emitters deposited in the lung and the bone. BEIR VII presents no risk estimates for radiogenic bone cancer. As in the past, we propose to estimate bone cancer risk from data on radium injected patients.

BEIR VII also fails to provide quantitative estimates of risk for skin cancer, both of which might be significant under some exposure conditions. Risks from prenatal

exposures are also not fully addressed by the report. BEIR VII presents a model for estimating radiogenic thyroid cancer incidence, but not thyroid cancer mortality. We hope to address these gaps and to consider the findings of an EPA sponsored thyroid report being drafted by the NCRP, when it becomes available.

As explained in Section II, we intend to employ somewhat different population statistics than BEIR VII. Consideration is given here to an alternative model for estimating radiogenic lung cancer, which diminishes what appears to be an anomalously high lung cancer risk projected in BEIR VII for females. For breast cancer, an alternative method is introduced for estimating mortality, which takes into account changes in incidence rates and survival rates over time.

BEIR VII provides quantitative uncertainty bounds for each of its risk coefficients. Nevertheless, in deriving these bounds, it is clear that some sources of uncertainty were not included. Most important, no uncertainty was assigned to the form of the dose-response relationship: it was implicitly assumed that the dose-response relationship is "linear-quadratic", which allowed the BEIR VII Committee to place uncertainty bounds on the "DDREF". Mechanisms pertaining to the biological effects of low level ionizing radiation are being investigated, which could eventually mandate a different dose-response model, with resulting large changes in estimates of risk at low doses. Assigning probabilities to alternative models would be highly subjective at this time. We do not propose to quantify the uncertainty pertaining to low-dose extrapolation, beyond what was done in BEIR VII, but we would expect to include a brief discussion of the issue in our revised risk assessment document.

II. Proposed Methods for Projecting Radiogenic Risk to the U.S. Population

A. Calculating Lifetime Attributable Risk

As in BEIR VII, we propose using lifetime attributable risk (LAR) as our primary risk measure. For a person exposed to dose (x) at age (e), the LAR is given by:

$$LAR(x,e) = \int_{e+L}^{110} M(x,e,a) \cdot S(a)/S(e)da \,. \qquad (1)$$

where

$M(x,e,a)$ is the excess absolute risk at attained age a from an exposure at age e, $S(a)$ is the probability of surviving to age a, and L is the latency period (2 years for leukemia, 5 years for solid cancers). The LAR approximates the probability of a premature cancer death from radiation exposure, and in BEIR VII (approximate) values for the LAR are obtained as weighted sums (over attained ages a up to age 100) of the excess probabilities of radiation-induced cancer incidence or death, $M(x,e,a)$. We intend instead to calculate the integral (Eq. 1) to age 110 (or perhaps 120) using spline approximations – not unlike the approach used to calculate EPA's current risk coefficients (EPA 1999).

The LAR for a population is calculated as a weighted average of the age-at-exposure specific risks discussed above. The weights are proportional to the number of people, $N(e)$, who would be exposed at age e. The population-averaged LAR is given by:

$$LAR(x, pop) = \frac{1}{N^*} \int_0^{110-L} N(e) \cdot LAR(x,e) \cdot de \,. \qquad (2)$$

For the BEIR VII approach, $N(e)$ is the number of people from census data in the U.S. population at age e for a reference year – BEIR VII used 1999, and N^* is the total summed over all ages. In contrast, for our primary projection, we propose to use a hypothetical stationary population for which the $N(e)$ are proportional to $S(e)$ based on observed mortality rates for the year 2000. Under the assumption that there would be no appreciable change in future mortality rates, this would approximate the radiogenic risk from a lifetime (chronic) exposure at constant dose rate. A stationary population is being used for our current risk assessment (EPA 1999).

B. Solid Cancer Incidence

For most cancer sites, separate evaluations of LAR were made using both an excess absolute risk (EAR) model and an excess relative risk (ERR) model. For most solid cancers (all but thyroid, and breast cancer), the ERR and EAR models were based exclusively on analyses of the atomic bomb survivor incidence data. This differs from

the risk models that had been used in previous risk assessments, and had been derived from mortality data.

Except for breast and thyroid cancers, the preferred BEIR VII EAR and ERR models are functions of sex, age at exposure, and attained age, and were of the form:

$$\text{EAR}(x,e,a) \text{ or } \text{ERR}(x,e,a) = \beta_s D \exp(\gamma e^*)(a/60)^{\eta},$$

$$\text{where } e^* = \frac{\min(e,30) - 30}{10}.$$

As seen in Table 1, the values for the parameters β_s, γ, and η depend on the type of model – EAR or ERR. For ERR models for most sites:

β, the ERR per Sv at age-at-exposure 30 and attained age 60, tends to be larger for females than males;
γ = -0.3 implies the radiogenic risk of cancer at age a falls by about 25% for every decade increase in age-at-exposure up to age 30; and
η = -1.4 implies the ERR is almost 20% smaller at attained age 70 than at age 60.

Thus, ERR decreases with age-at-exposure (up to age 30) and attained age. In contrast, for EAR models for most sites, γ = -0.41 and η = 2.8. EAR decreases with age-at-exposure but 12-1A (NAS 2006, increases with attained age. These patterns are illustrated in BEIR VII (NAS 2006, Figure 12.1A, p. 270).

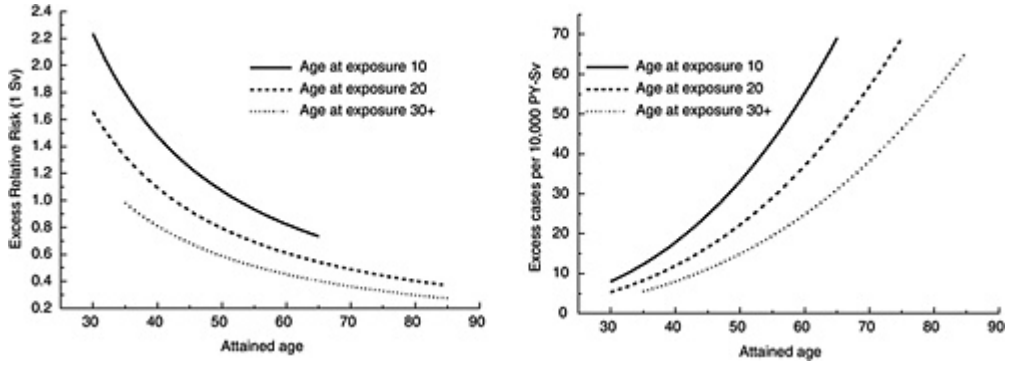

FIGURE 12-1A Age-time patterns in radiation-associated risks for solid cancer incidence excluding thyroid and nonmelanoma skin cancer. Curves are sex-averaged estimates of the risk at 1 Sv for people exposed at age 10 (solid lines), age 20 (dashed lines), and age 30 or more (dotted lines). Estimates were computed using the parameter estimates shown in Table 12-1 of BEIR VII. FROM BEIR VII

For either type of model, calculating the LAR is relatively straightforward. For the EAR models, note that $M(x,e,a) = \text{EAR}(x,e,a)$. For ERR models,

$$M(x,e,a) = ERR(x,e,a) \cdot \lambda_I(a),$$

where $\lambda_I(a)$ is the baseline cancer incidence rate at age *a*. Values for LAR are then obtained using equations 1 and 2.

Results of LAR calculations are given in Table 2. Separate calculations were made using both census data – weights proportional to the number of people of each age in the year 2000, and a stationary population – based on mortality data for the year 2000. For most sites, the LAR is about 5-10% larger when based on weights from census data.

Table 1: Parameter values for preferred risk models in BEIR VII[1]

Cancer	ERR model				EAR model			
	β_M	β_F	γ	η	β_M	β_F	γ	η
Stomach	0.21	0.48	-0.3	-1.4	4.9	4.9	-0.41	2.8
Colon	0.63	0.43	-0.3	-1.4	3.2	1.6	-0.41	2.8
Liver	0.32	0.32	-0.3	-1.4	2.2	1	-0.41	4.1
Lung	0.32	1.4	-0.3	-1.4	2.3	3.4	-0.41	5.2
Breast	Not used				See text			
Prostate	0.12		-0.3	-1.4	0.11		-0.41	2.8
Uterus		0.055	-0.3	-1.4		1.2	-0.41	2.8
Ovary		0.38	-0.3	-1.4		0.7	-0.41	2.8
Bladder	0.5	1.65	-0.3	-1.4	1.2	0.75	-0.41	6
Other solid	0.27	0.45	-0.3	-2.8	6.2	4.8	-0.41	2.8
Thyroid[2]	0.53	1.05	-0.83	0	Not used			

[1] From Table 12-2 (NAS 2006)
[2] Unlike other sites, the dependence on ERR on age-at-exposure is not limited to ages < 30y.

Table 2: Comparison of the impact of two methods for age-averaging on LAR for solid cancer incidence for selected sites. Projections are made using the BEIR VII EAR and ERR models. Age-averaging is based on either 2000 census data (NCHS 2004) or a stationary population constructed from 2000 life tables (Arias 2002).

		Risk Model Population Weighting			
		EAR		ERR	
Site	Sex	Census	Stationary	Census	Stationary
Stomach	Male	278	259	23	22
	Female	328	308	30	29
Colon	Male	182	169	256	240
	Female	107	100	164	155
Liver	Male	150	141	25	23
	Female	84	80	9	9
Lung	Male	189	179	246	230
	Female	361	344	767	714
Breast	Female	463	423	507	465
Prostate	Male	6	6	202	187
Uterus	Female	80	75	16	15
Ovary	Female	47	44	75	69
Bladder	Male	121	115	170	160
	Female	101	96	165	155

NOTE: Number of cases per 100,000 persons exposed to 0.1 Gy.

C. Solid Cancer Mortality

The ERR and modified versions of the EAR models just discussed were used in BEIR VII to calculate LAR for radiation-induced cancer death. For ERR, the same models were used for both incidence and mortality,

$$M(x,e,a) = ERR(x,e,a) \cdot \lambda_M(a).$$

For EAR, BEIR VII used essentially the same approach by assuming

$$M(x,e,a) = \frac{EAR(x,e,a)}{\lambda_I(a)} \lambda_M(a) \quad . \qquad (3)$$

Note that the ratio of age-specific EAR to incidence rate is the ERR for incidence – based on the EAR model. Equations (1) and (2) are then applied to obtain the LAR. This BEIR VII approach, equating the incidence and mortality ERR, ignores the "lag" between incidence and mortality, which could lead to bias in the estimate of mortality risk in at least two different ways.

First, there would be a corresponding lag between the ERR for incidence and mortality, which might result in an underestimate of mortality risk. For purposes of illustration, suppose that a particular cancer is either cured without any potential life-shortening effects or results in death exactly 10 years after diagnosis, and that survival does not depend on whether it was radiation-induced. Then, with subscripts *M* and *I* denoting mortality and incidence:

$$ERR_M(x,e,a) = ERR_I(x,e,a\text{-}10) > ERR_I(x,e,a).$$

The same relationship would hold for EAR, if the baseline cancer rate has the same age-dependence for A-bomb survivors as for the U.S. population.

Second, since current cancer deaths often occur because of cancers that develop years ago, application of the EAR-based ERR for incidence can result in a substantial bias due to birth cohort effects. If age-specific incidence rates increase (decrease) over time, the denominator in Equation 3 would be too large (small). This could result in an underestimate (overestimate) of the LAR.

The BEIR VII approach is reasonable for most cancers, because the time between diagnosis and a resulting cancer death is typically short. An exception is breast cancer, and an alternative approach is outlined in Section H.

Results of LAR calculations using the BEIR VII approach are given in Table 3. Similar to what was observed for incidence, LAR for mortality tends to be about 5% larger using census-based weights than for weights based on a stationary population. Mortality and incidence data used for the calculations are described in the next section.

Table 3: Comparison of impact of two methods for age-averaging on LAR for solid cancer mortality for selected sites. Projections are made using the BEIR VII EAR and ERR models. Age-averaging is based on either 2000 census data (NCHS 2004) or a stationary population constructed from 2000 life tables (Arias 2002).

		Risk Model Population Weighting			
		EAR		ERR	
Site	Sex	Census	Stationary	Census	Stationary
Stomach	Male	146	136	12	11
	Female	183	173	17	16
Colon	Male	84	79	119	113
	Female	47	44	72	69
Liver	Male	114	108	17	16
	Female	70	66	7	7
Lung	Male	179	169	229	214
	Female	312	298	618	577
Breast	Female	103	94	101	94
Prostate	Male	1	1	32	30
Uterus	Female	19	18	3	2
Ovary	Female	27	26	36	34
Bladder	Male	28	27	34	32
	Female	33	32	43	41

NOTE: Number of deaths per 100,000 persons exposed to 0.1 Gy

D. U.S. Baseline and Census Data

Cancer specific incidence and mortality rates are based on the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI). Begun in the early 1970's, SEER collects data from several mostly statewide and metropolitan cancer registries within the U.S. Rates for this report are calculated using SEER-Stat and the 1975-2003 SEER public-use data (SEER 2006a,b) available from the SEER website (http://seer.cancer.gov). The dataset is structured to represent two notable expansions in the SEER program: from 9 registries to 13 registries (SEER 13) in the early 1990's and most recently to 17 registries (SEER 17). For this report, incidence rates for each 5 year age-interval are the average of data for the years 1998-2000 from SEER 13, and SEER 17 data for the years 2000-2002. This contrasts with BEIR VII, which used (a previous version) of public-use SEER 13 data for the years 1995-99.

SEER regularly revises its statistics on baseline rates, and the baseline rates used for our final risk assessment will likely be based on SEER statistics for the year 2000 that

are not yet available. For example, it is anticipated that the denominator (person years at risk) for future versions of the SEER cancer data will be derived using 2000 decennial census results.

SEER areas currently comprise about 26% of the U.S. population, and are not a random sample of areas within the U.S. Nevertheless the cancer rates observed in the combined SEER areas are thought to be reasonably similar to rates for the U.S. population. For the final risk assessment, datasets that would reflect a much larger area than SEER represents will also be considered, such as data that incorporates the CDC National Program of Cancer registries.

Finally, we used life tables for the year 2000 (compared to 1999 for BEIR VII), (Arias 2002) available at http://www.cdc.gov/nchs/data/lt2000.pdf. Life tables for our final risk assessment will likely be based on NCHS data that incorporates data from the decennial census.

Changes in any of these data sets for the final risk assessment will likely have only minor changes in risk projections.

E. Combining Results from ERR and EAR Models

1. BEIR VII approach

BEIR VII calculates LAR values separately based on preferred EAR and ERR models, and then combines results using a weighted geometric mean. More specifically:

$$LAR_{B7} = (LAR_R)^w (LAR_A)^{1-w},$$

with weight (w) – on results from the ERR model – depending on cancer site. If a weight (w) equals 0.5, a simple geometric mean would be calculated. Instead for most cancer sites, BEIR VII recommended weights (w) equal to 0.7 – placing somewhat more emphasis on results from ERR models. (A notable exception is lung cancer where the EAR model is given more weight, reflecting near additivity between smoking and gamma radiation in the A-bomb survivor data.)

A problem with the BEIR VII method for averaging the EAR and ERR projections is that the geometric mean is not additive in the sense that the geometric mean of two risk projections for the combined effect of separate exposures is generally not equal to the sum of the geometric mean projections for the exposures. We circumvent this problem by first calculating the weighted geometric mean of the excess absolute risk for the two projection models for each at each age at exposure and attained age. Then, results can be integrated to calculate risk from chronic lifetime exposure.

2. Proposed EPA approach

Thus, we propose calculating the combined age-specific risk (at high dose rates) according to:

$$M_C(x,e,a) = [M_A(x,e,a)]^w [M_R(x,e,a)]^{1-w},$$

with the LAR at exposure age *e* calculated as before:

$$LAR_C(x,e) = \int_{e+L}^{110} M_C(x,e,a) \cdot S(a)/S(e) da$$

The difference with the BEIR VII approach is that the risk models would be combined ***before*** integrating results according to (1) to obtain the *LAR*.

The two methods of combining results from EAR and ERR models, BEIR VII and the proposed EPA approach, are compared in Table 4. The method of combination has only a minimal impact on age-averaged LAR calculations.

Table 4: Comparison of proposed and BEIR VII method for combining EAR and ERR LAR projections for incidence.[1]

		Method of Combination	
Site	**Sex**	**Proposed**	**BEIR VII**
Stomach	Male	45	46
	Female	58	58
Colon	Male	214	216
	Female	135	136
Liver	Male	38	39
	Female	17	17
Lung	Male	186	193
	Female	401	428
Breast	Female	423	423
Prostate	Male	63	66
Uterus	Female	115	120
Ovary	Female	58	60
Bladder	Male	141	145
	Female	129	134

NOTE: Number of cases per 100,000 persons exposed to 0.1 Gy

[1]Results are shown for stationary populations and SEER incidence data for the years 1998-2002.

F. Cancer Sites with Individual Risk Estimates

With few exceptions, we agree with BEIR VII's choice of sites for individual risk projections. BEIR VII cited two main criteria for deciding on the sites for which individual risk projections should be provided. First, the cancer should be linked clearly with radiation exposure, and second, there should be adequate data to develop reliable risk estimates. In our view, these criteria are generally reasonable. Leukemia and cancers of the stomach, colon, liver, lung, breast, bladder, ovary and thyroid all satisfy the first and arguably both criteria. In addition, BEIR VII also provides individual projections for cancers of the uterus and prostate. In our view, the choice of uterine cancer is appropriate. The A-bomb survivor data provides sufficient information for radiogenic uterine cancer to formulate a risk projection of reasonable precision. Regarding prostate cancer, BEIR VII cites the vastly differing baseline rates for the U.S. compared to Japan for providing a separate prostate estimate. The BEIR VII estimate for prostate cancer – based on data that includes less than 300 cancers – is unreliable, being essentially dominated by the effects of sampling error. Nevertheless, at this point, we anticipate adopting the BEIR VII model for prostate cancer. As discussed elsewhere, we plan to provide individual estimates for bone cancer and possibly non-melanoma skin cancer. A discussion of possible changes to the application of the BEIR VII models for projecting radiogenic lung cancer risks follows.

G. Possible Modifications for Radiogenic Lung Cancer Risk Projections

In our view, the BEIR VII lung cancer ERR model might not be appropriate for projecting radiogenic risk to the U.S. population. The BEIR VII ERR projection is based upon a fit to the A-bomb survivor data without any adjustment for smoking, which distorts the ERR for radiogenic lung cancer. This is due to substantial birth-cohort related changes in smoking habits among cohort members, and the likelihood that the effects of smoking and radiation are approximately additive (Pierce et al. 2003). Thus, without adjustment for smoking, observed ERR values in the A-bomb cohort are largest for early birth cohorts who smoked less and had lower baseline lung cancer rates, but may have similar absolute risks from radiation as other survivors. This would distort the age-at-exposure effect on radiogenic risk because the observed ERR would tend to be an overestimate for older ages-at-exposure (early birth dates) as compared to younger ages-at-exposure (later birth dates). Pierce et al. also discuss how – without adjustment for smoking – attained-age effects might also be distorted.

Overall, the modeled ERR for radiogenic lung cancer in the A-bomb cohort would be higher than might be appropriate for the U.S. population. Based on evidence that radiation and smoking are roughly additive in the A-bomb survivors, the absolute risk from radiation would be similar in the U.S. and Japan. However, the U.S. smoking-related lung cancer rates would almost surely be substantially higher than had been observed in the A-bomb cohort.

Not accounting for smoking also affects the estimate of the female:male sex ratio (β_F / β_M), about 4.4 for the BEIR VII ERR models. This is why BEIR VII's ERR-based LAR is much larger for females (0.074 per Gy) than for males (0.026 per Gy). Using a subset of the LSS for which smoking information was available, Pierce et al. found that "after adjusting for smoking, the radiation-related risks relative to background rates for nonsmokers are similar to those for other solid cancers: a sex-averaged ERR/Sv of about 0.9 with a female:male sex ratio of about 1.6. Adjusting for smoking removes a spuriously large female:male ratio in radiation relative risk due to confounding between sex and smoking level."

The BEIR VII EAR model would not seem to suffer from the same birth-cohort related effects that distort the ERR observed in the A-bomb survivors. Given that lung cancer rates are driven predominantly by smoking patterns, and the evidence for additive effects of smoking and radiation, an EPA projection based exclusively on the BEIR VII EAR model should be considered.

Another approach for estimating the LAR, suggested by Pierce et al. (p. 519) is as follows: "Lifetime risk computations involve estimating age-specific absolute lung cancer rate increases and then summing these over age with weights corresponding to the chance of survival to each age. The absolute rate increases may best be estimated by multiplying lung cancer rates for nonsmokers and the ERR/Sv relative to nonsmokers." Although there are some compelling arguments for this approach, reasons not to use it include: 1) the apparent presumption that factors (such as radon) – other than smoking – are multiplicative with low-LET radiation; 2) ambiguity as to whether non-smokers includes (any) former smokers; 3) difficulty in estimating baseline never- or non-smoker lung cancer rates.

H. Calculating Radiogenic Breast Cancer Mortality Risk

This section outlines an alternative method for calculating radiogenic breast cancer risk, compares results with calculations based on the BEIR VII method, and indicates potential additional modifications.

As before, $M(x, e, a_C)$ denotes the excess absolute risk at attained age a_C from an exposure at age *e*. The density function for radiogenic cancer at a_c would be:

$$C(x, e, a_c) = M(x, e, a_c)\, S(a_c) / S(e)\,.$$

For the cancer to result in a death at age $a > a_C$, the patient would have to survive the interval (a_C , *a*), and then die from the cancer at age *a*. This and the concept of the relative survival rate form the basis for the method. The relative survival rate for a breast cancer patient would be the ratio of the survival rate for the patient divided by the expected survival rate (without breast cancer). Assuming that the relative survival depends only on the length of the time interval and is independent of age of diagnosis,

and letting $R(t)$ be the relative survival function, the probability of survival with breast cancer for the interval (a_c, a) would be:

$$S(a)/S(a_c)R(a-a_c).$$

Furthermore, assuming the breast cancer mortality rate among those with breast cancer (h) does not depend on age, the density function for breast cancer death can be shown to equal:

$$D(x,e,a) = \int_0^a C(x,e,a_c)\, S(a)/S(a_c)R(a-a_c)h\, da_c .$$

Baseline mortality rates can be derived in a similar manner. Baseline lifetime breast cancer mortality risk and lifetime LAR estimates are compared in Table 5. The rate *h* was set to 0.0233, corresponding to a 5 year relative survival rate of about 0.89 (Ries et al. 2006).

Table 5: Baseline lifetime risks and LAR for breast cancer mortality.

Method	Baseline lifetime risk	Lifetime LAR
BEIR VII	2990	92
EPA Alternative	4630	126

NOTE: Number of deaths in a population of 100,000 persons. LAR for exposures of 0.1 Gy.

Much of the discrepancy between the two sets of results seems to be a consequence of observed increases in breast cancer incidence rates and declines in mortality rates. From 1980 to 2000, age-averaged breast cancer rates increased by about 35% (102.1 to 135.7), whereas the mortality rates declined by about 15% from 31.7 to 26.6 (http://seer.cancer.gov/csr/1975_2003/results_merged/sect_04_breast.pdf).

To understand the possible implications of the trends in incidence and mortality on the alternative LAR calculations, consider the assumptions on which the projections are based:

The BEIR VII projection is based on the following formula:

$$M(x,e,a) = EAR(x,e,a)\frac{\lambda_M(a)}{\lambda_I(a)} .$$

Essentially, the absolute risk of radiogenic cancer death from an exposure at age *e* is assumed to be equal to the absolute risk of a radiation-induced cancer multiplied by a lethality ratio (that depends on attained age). In BEIR VII, the lethality ratio is estimated as the ratio of current mortality rates divided by current incidence rates. However, since

would seem to be best determined by comparing current mortality rates to incidence rates observed for (much) earlier time periods. If as data indicate, current incidence rates are much larger than past incidence rates, the BEIR VII denominator is too large, and the estimated lethality ratio is too small. In contrast, the BEIR VII calculation of lifetime baseline mortality risk is a valid estimate of risk with respect to current mortality rates, since in particular it does not depend on an estimate of lethality. Of course, it is only a snapshot reflecting the overall rates of breast cancer deaths currently observed for all U.S. women, and would not be a reliable indicator of future breast cancer mortality (that might result from currently diagnosed cases).

The proposed EPA alternative projection also has limitations. The validity of the projections would depend on the extent to which estimates of relative survival functions can be used to approximate mortality rates from breast cancer for people with breast cancer. There are two potential problems with this approach which merit further investigation:

One relates to the improvement in survival rates for women with breast cancer. Long-term survival rates for breast cancer patients are needed to construct valid estimates for this approach, but since these survival rates can change rapidly, extrapolation of rates for periods beyond 5 to 10 years may be unreliable. The relative survival rates upon which the estimates in Table 5 were based reflect "current" rates, and were constructed from SEER data for 1996-2002. Although a simple exponential function seems to be a very good approximation to the relative survival up to 5 years, there is no guarantee as to how appropriate such an approximation would be for (extrapolation to) longer time periods. It should be noted that the alternative "EPA" estimate of baseline lifetime risk for breast cancer mortality reflects current incidence rates and "current" (short-term) breast cancer survival rates. In contrast to the BEIR VII estimate of baseline risk, such an approach may result in a valid estimate of mortality from currently occurring cases to the extent that long-term rates can be approximated – based on extrapolations – from recent data.

The other problem is that the reduced expected survival among breast cancer patients may be partly attributable to causes other than breast cancer. For example, if some breast cancers are smoking-related, breast cancer patients as a group may be at greater risk of dying from lung cancer.

I. Leukemia

We plan to adopt the approach used in BEIR VII with only minor modifications. Calculations would be based on the BEIR VII ERR and EAR models:

$$EAR(x,e,a,t) \text{ or } ERR(x,e,a,t) = \beta_S x(1+\theta x)\exp[\gamma e^* + \delta \log(t/25) + \phi e^* \log(t/25)],$$

where t is time since exposure. We would use the parameter values recommended in BEIR VII (Table 12-3). LAR would be calculated using the same methodology proposed

where *t* is time since exposure. We would use the parameter values recommended in BEIR VII (Table 12-3). LAR would be calculated using the same methodology proposed for most solid cancer sites. Following the BEIR VII recommendation, a DDREF of 1 will be assumed. Departures from the BEIR VII methods include: (1) calculating a weighted geometric mean of the excess absolute risk for the two projection models for each at each age at exposure and attained age, and (2) using weights based on a stationary population for our primary projection.

J. Preliminary Risk Calculations

Table 6 compares LAR calculations for selected solid cancers based on the proposed EPA methods with calculations in BEIR VII. With the exception of lung cancer, the proposed EPA methods are based on the same EAR and ERR models as in BEIR VII . For lung cancer, the BEIR VII ERR model would not be used.

Table 6: Comparison of proposed EPA and BEIR VII LAR calculations.

		Incidence		Mortality	
Site	**Sex**	**EPA**	**BEIR VII**	**EPA**	**BEIR VII**
Stomach	Male	30	34	16	19
	Female	39	43	22	25
Colon	Male	143	160	67	76
	Female	90	96	40	46
Liver	Male	25	27	18	20
	Female	11	12	9	11
Lung[1]	Male	119	140	113	140
	Female	229	300	199	270
Breast	Female	282	310	84[2]	73
Prostate	Male	42	44	8	9
Uterus	Female	15	20	3	5
Ovary	Female	39	40	20	24
Bladder	Male	94	98	20	22
	Female	86	94	25	28

NOTE: Number of deaths or cases per 100,000 persons exposed to 0.1 Gy.

[1]EPA projection of lung cancer based on BEIR VII EAR model.
[2]EPA projection based on alternative method as described in the previous section.

K. Uncertainties

The BEIR VII Report includes a quantitative uncertainty analysis with 95% subjective CIs for each site-specific risk estimate. The analysis focused on three sources

uncertainty in the appropriate value of a DDREF for projecting risk at low doses and dose rates from the LSS data.

The BEIR VII analysis neglected other sources of uncertainty, including: (1) errors in dosimetry; (2) errors in disease detection and diagnosis; (3) uncertainty in the age and temporal pattern of risk, especially for individual sites, which was usually taken to be the same as that derived for all solid tumors; (4) uncertainty in the relative effectiveness of medical x rays in inducing cancer for those sites where data on medically irradiated cohorts were used in deriving the risk models.

It should also be noted that the treatment of uncertainty in projecting risk at low doses and dose rates of low-LET radiation, basically *assumes* the "linear-quadratic" dose-response model in which: (1) the risk from an acute dose, D, is of the form $\alpha D + \beta D^2$ and (2) the risk from low dose rate radiation is then simply αD. The assumption here that one can extrapolate risk linearly from moderate acute doses (≈100 mGy) to very low dose fractions remains contentious.

EPA proposes adopting the BEIR VII quantitative uncertainty bounds for most purposes. It is anticipated, however, that the revised Blue Book would contain an examination of where these uncertainty bounds might fail to adequately capture the overall uncertainty. In addition, we would include a brief discussion of the low dose extrapolation problem, which would acknowledge continuing disagreement on this issue.

Ultimately, the estimates of uncertainties in risk per unit dose can be combined with estimates of uncertainties in tissue doses for internally deposited radionuclides in order to obtain uncertainty estimates for inhaled or ingested radionuclides. For alpha emitting radionuclides this will require additional assessment of risk and uncertainty beyond what is contained in BEIR VII. Estimation of risk from internally deposited alpha emitters is addressed in the next section.

III. Risks from Higher LET Radiation

A. Alpha Particles

Assessing the risks from ingested or inhaled alpha-emitting radionuclides is problematic from two standpoints. First, it is often difficult to accurately estimate the dose to target cells, given the short range of alpha-particles in aqueous media (typically < 100 μm) and the often non-uniform distribution of a deposited radionuclide within an organ or tissue. Second, there is very little direct human data on cancer induction by alpha particles. For most tissues, the risk to a given tissue from a given dose of alpha radiation must be calculated based on the estimated risk from an equal absorbed dose of γ rays multiplied by an "RBE" factor that accounts for different carcinogenic potencies of the two types of radiation, derived from what are thought to be relevant comparisons in experimental systems

The high density of ionizations associated with tracks of alpha radiation produces DNA damage which is less likely to be faithfully repaired than damage produced by low-LET tracks. Consequently, for a given absorbed dose, the probability of inducing a mutation is higher for alpha radiation, but so is the probability of cell killing. The effectiveness of alpha radiation relative to some reference low-LET radiation (e.g., 250 kVp x rays or ^{60}Co γ rays) in producing some particular biological end-point is referred to as the alpha-particle relative biological effectiveness (RBE). The RBE may depend not only on the observed end-point (induction of chromosome aberrations, cancer, etc.), but also on the species and type of tissue or cell being irradiated, as well as dose and dose rate.

In most experimental systems, the RBE increases with decreasing dose and dose rate, apparently approaching a limiting value. This mainly reflects reduced effectiveness of low-LET radiation as dose and dose rate are decreased–presumably because of more effective repair. In contrast, the effectiveness of high-LET radiation in producing residual DNA damage, transformations, cancer, etc. may actually decrease at high doses and dose rates, at least in part due to the competing effects of cell killing. For both low- and high-LET radiations, it is posited that at low enough doses, the probability of a stochastic effect is proportional to dose, and independent of dose rate. Under these conditions, the RBE is maximal and equal to a constant RBE_M. In order to estimate site-specific cancer risks for low dose alpha radiation, we need a low-dose, low-LET risk estimate for that site and an estimate of the RBE_M.

1. Laboratory studies

The experimental data on the RBE for alpha particles and other types of high-LET radiation have been reviewed by the NCRP (NCRP 1990) and the ICRP (ICRP 2003). From laboratory studies, the NCRP concluded that: "The effectiveness of alpha emitters is high, relative to beta emitters, being in the range of 15 to 50 times as effective for the induction of bone sarcomas, liver chromosome aberrations, and lung cancers." The

NCRP made no specific recommendations on a radiation weighting factor for alpha radiation.

The ICRP has reiterated its general recommendation of a radiation weighting factor of 20 for alpha-particles (ICRP 2003, 2005). However, ICRP Publication 92 further states (ICRP 2003):

> Internal emitters must be treated as a separate case because their RBE depends not merely on radiation quality, but also, and particularly for α-rays with their short ranges, on their distribution within the tissues or organs. It is, accordingly, unlikely that a single w_R should adequately represent the RBE_M for different α emitters and for different organs…The current w_R of 20 for α-rays can thus serve as a guideline, while for specific situations, such as the exposure to radon and its progeny, or the incorporation of ^{224}Ra, ^{226}Ra, thorium, and uranium, more meaningful weighting factors need to be derived.

Another set of recommendations for α-particle RBE is contained in the NIOSH-Interactive RadioEpidemiological Program (NIOSH-IREP) Technical Documentation meant for use in adjudicating claims for compensation of radiogenic cancers (NIOSH 2002, Kocher et al. 2005). IREP posits a lognormal uncertainty distribution for its radiation effectiveness factor (REF, equivalent to RBE_M) with a median of 18 and a 95% CI [3.4, 101]. For leukemia, IREP employs a hybrid distribution: REF=1.0 (25%); =LN(1,15) (50%); =LN(2,60) (25%) where LN(a,b) represents a lognormal distribution with a 95% CI of [a,b].

Studies comparing groups of animals inhaling insoluble particles to which are attached alpha or beta emitters have been performed to assess RBE for lung cancer. In a large long-term study of beagle dogs, Hahn et al. (1999) reported that the RBE was at least 20. In contrast, from an analogous study of lung cancer induction in CBA/Ca mice, Kellington et al. (1997) estimated the RBE to be only 1.9.

2. Human data

Results from epidemiological studies of groups exposed to alpha radiation can be used, directly, to develop risk estimates for alpha radiation; they can also be used in conjunction with low-LET studies to estimate RBE; finally, it is possible to use results from these studies in combination with estimates of RBE to derive low-LET risk estimates where none can be obtained from low-LET studies.

There are four cancer sites for which we have direct epidemiological evidence on the risks from alpha irradiation: bone, bone marrow, liver, and lung. In each of these cases except for bone, we also have risk estimates for low-LET radiation derived from the LSS.

Bone Cancer. Although there is some new information coming from research on Mayak plutonium workers, the most definitive information on bone cancer risk continues to be radium dial painters exposed to ^{226}Ra and ^{228}Ra and patients injected with the shorter-lived isotope ^{224}Ra. The usefulness of the dial painter data for low dose risk estimation suffers from lack of complete epidemiological follow-up and from the

possible complicating effects of extensive tissue damage associated with very high doses of radiation in the bone. For this reason, EPA has taken its estimates of risk of alpha-particle-induced bone sarcoma from the BEIR IV analysis of the ^{224}Ra data, which is consistent with a linear, no-threshold dose response (NRC 1988, EPA 1994). The corresponding low-LET risk estimate (per Gy) was assumed to be a factor of 20 lower based on the assumed alpha-particle RBE_M of 20. We believe that no major change in bone cancer incidence risk estimates is warranted; some downward adjustment of mortality estimates may be warranted to reflect improved survival.

Leukemia. Excess leukemia cases have not been observed in studies of radium dial painters or patients injected with ^{224}Ra, although in some cases there was evidence of some blood disorders that may have been undiagnosed leukemias. It is clear from these studies, however, that bone sarcoma is a more common result of internally deposited radium, and that the radium leukemia risk is much lower than that calculated using ICRP dosimetry models together with a leukemia risk coefficient derived from the LSS weighted by an RBE of 20. As with humans, it appears that Ra isotopes induce bone cancers but few if any leukemias. In part, the low incidence of leukemia might be attributed to microdosimetry: i.e., target cells may be non-uniformly distributed in the bone marrow in such a way that the dose to these cells is considerably lower than the average marrow dose.

Evidence suggests, however, that microdosimetry is not the full story, and that high-LET radiation is only weakly leukemogenic. Thorotrast patients, who are expected to have a more even distribution of alpha-particle energy, do show an excess of leukemia, but only about twice the risk per Gy as seen in the LSS (ICRP 2003). Moreover, an RBE of only about 2.5 has been found for neutron induced leukemia in mice (Ullrich and Preston 1987). BEIR VII low-LET risk estimate for leukemia incidence is roughly 50% higher than that of UNSCEAR or EPA. Using a Bayesian approach, Grogan et al. (2001) estimated the alpha-particle leukemia risk to be 2.3×10^{-2} Gy^{-1}. Based on the BEIR VII low-LET leukemia (incidence) risk estimate, this would correspond to an RBE of approximately 2.5. Through a comparison of Thorotrast and A-bomb survivor data, Harrison and Muirhead (2003) also estimated the RBE to be 2-3. However, the authors noted that the Thorotrast doses were likely to be overestimated by a factor of 2-3 (Ishikawa et al. 1999), and that the RBE was perhaps very close to 1. EPA has been employing an RBE of 1 for leukemia; it would appear that a value of about 1-3 is still reasonable.

Liver. The LSS study shows a statistically significant excess of liver cancer. The uncertainty bounds derived by BEIR VII are wide, both because of the large sampling error and the uncertainty in the population transport (liver cancer rates are about an order of magnitude lower here than in the LSS cohort). The BEIR VII central estimate is $\approx 2 \times 10^{-3}$/Gy. For comparison, an update on Danish Thorotrast patients (Andersson et al.1994) yielded an estimate of 7×10^{-2} per Gy. Thus, given the large uncertainties and difference in age and temporal distribution, these findings are reasonably consistent with the commonly assumed default value of 20 for alpha-particle RBE. Grogan et al. (2001) also concluded that a value of 20 (GM) with 1.6 GSD was the best estimate of an RBE

relative to γ rays based on the follow-up of the Thorotrast patients and the atomic bomb survivors.

We conclude that the use of the liver cancer risks in BEIR VII, modified by an RBE of 20, provides a suitable estimate of the risk alpha-particle induced liver cancer. Uncertainty estimates will require consideration of both uncertainties in the BEIR VII estimates and the uncertainty in RBE.

Lung. Excess lung cancers have been associated with the inhalation of alpha-emitting radionuclides in numerous epidemiological studies. Cohort studies of underground miners and residential case-control studies have shown a strong association with exposure to airborne radon progeny. In addition, a cohort study of workers at the Mayak nuclear plant, has also shown an association with inhaled plutonium (Gilbert et al. 2004). The miner studies serve as the primary basis for BEIR VI and EPA estimates of risk from radon exposure (NRC 1999, EPA 2003), and results from the residential studies are in reasonable agreement with those risk estimates (Darby et al. 2005, Krewski et al. 2005). The Agency has no plans at this time to reassess its estimates of risk from exposure to radon progeny, but it is our intent to reassess estimates of risk from inhaled plutonium and other alpha-emitters, along with the lung cancer risk associated with low-LET exposures.

Table 7 compares summary measures of risk per unit dose for the U.S. population derived from the LSS in BEIR VII and from the pooled underground miner studies in BEIR VI. The RBE inferred from this comparison is much lower than what one might project based on most animal studies. It should be recognized, however, that the risk model used to derive risk estimates for radon are in certain ways incompatible with the models for low-LET lung cancer risk in BEIR VII. They differ not only with respect to age, gender, and temporal factors, but also with respect to the interaction with smoking. In contrast to the BEIR VII models, the radon risk models do not incorporate a higher risk coefficient for females or for children. The miner cohorts from the radon models were derived consisted essentially entirely of adult males, and it is possible that radon risks are being underestimated for children and females. On the other hand, results from residential case-control studies on females are generally consistent with projections based on the miners. The radon risk appears to be almost multiplicative with smoking risk (or the baseline lung cancer rate), whereas the LSS data suggests an additive interaction. It is unclear whether these apparent differences with respect to gender and smoking reflect a real mechanistic difference in carcinogenesis by the two types of radiation exposure (chronic alpha versus acute gamma) or unexplained errors inherent in the various studies.

Table 7: Lung cancer mortality and RBE.

Source of Data	Gender	Risk per 10^6 Person-WLM	Risk per 10^4 Person-Gy	RBE
A-bomb mortality	Male	-----	140 (52, 380)[2]	1.0
	Female	-----	270 (110, 660)[2]	1.0
	Combined	-----	210	1.0
EPA radon risk model	Male	640	800[1]	5.7
	Female	440	350[1]	1.3
	Combined	540 (*220, 1300*)[3]	430[1]	2.0

[1] Risk per Gy to the whole lung, assuming: (1) 12 mGy/WLM, on average, to sensitive cells in the bronchial epithelium (James, Birchall & Akabani) and (2) lung risk partitioned 1/3 (bronchi):1/3 (bronchioles):1/3 (alveoli).
[2] 95% C.I. (NRC 2006)
[3] 90% C.I. (EPA 2003)

Table 8 compares lung cancer results from the LSS with those on Mayak workers, whose lungs were irradiated by alpha particles emitted by inhaled plutonium. Some issues also arise here in trying to compare ERR/Gy and EAR/Gy estimates from the two studies. One is that the populations are quite different with respect to gender and age profile. Males account for about 75% of the PY and over 90% of the lung cancers among the internally exposed Mayak workers, but for only about 30% and 55% of the PY and lung cancers, respectively, among the LSS cohort. Another is that the dependence of the risk on attained age appears to be quite different in the two studies---a monotonically increasing EAR for the LSS but a sharp decrease in the EAR above age 75 for the Mayak workers. There are, however, very few data on these older Mayak workers. Focusing just on lung cancers appearing between ages 55 and 75, one finds that the central estimates of risk per Sv in the two studies are comparable, consistent with an RBE for alpha particles of 10 or more.

The risk per unit dose estimate from the plutonium exposed Mayak workers is considerably higher than that from the radon studies. This is somewhat surprising since the lung dose from radon progeny is projected to be almost entirely to the epithelial lining of the airways, whereas the inhaled plutonium dose would be expected to be concentrated in the alveoli, which is generally thought to be a much less sensitive region for cancer induction.

Table 8

Estimated Parameters for Lung Cancer Mortality Risks with 95% Confidence Intervals (CI) for Internal Lung Dose in Mayak Workers and External Lung Dose in the Life Span Study (LSS) Cohort of Japanese Atomic Bomb Survivors Exposed between the Ages of 15 and 60

	Mayak workers			LSS cohort age 15–60 at exposure		
	Person-years[a] (percentage of total)	Lung cancer deaths[a]	ERR per sievert[b] at attained age 60[c] (95% CI)	Person-years (percentage of total)	Lung cancer deaths	ERR per sievert at attained age 60[c] (95% CI)
Total	306,505	374		1,797,201	1,130	
By sex						
Males	231,473 (76)	343	0.23 (0.16; 0.33)	566,926 (32)	622	0.40 (0.032; 0.86)
Females	75,032 (24)	31	0.93 (0.46; 1.9)	1,230,277 (68)	508	1.40 (0.76; 2.2)
Female/male ratio			4.0 (1.9; 8.8)			3.6 (1.2; 11)
By attained age			Excess deaths per 10^4 PY-Sv[b] (95% CI) (males[d])			Excess deaths per 10^4 PY-Sv (95% CI) (both sexes)
Under 55 years	209,332 (68)	63	1.4 (0.77; 2.3)	763,044 (42)	46	0 (<0; 0.53)
55–64 years	62,990 (21)	154	5.1 (3.5; 7.1)	442,429 (25)	167	1.5 (<0; 3.8)
65–74 years	29,558 (9.7)	133	5.2 (2.6; 8.6)	370,558 (21)	400	7.2 (3.4; 11.9)
75+ years	4,595 (1.5)	24	1.4 (<0; 12)	221,170 (12)	517	14.3 (6.6; 23.7)
Mean age	48	63		57	73	

[a] Including only person-years and lung cancer deaths where internal lung doses could be estimated; however, all workers and person-years were included in the analyses.

[b] Sieverts were calculated by dividing the dose in grays by a quality factor (QF) of 20.

[c] Based on a model in which the coefficient of the logarithm of attained age was set equal to −2.2.

[d] EAR for females would be a factor of 0.43 smaller than these estimates.

There seems to be no fully satisfactory way to reconcile all the results from the LSS, miner and Mayak worker studies with what one would expect from the dosimetry and experimental determinations of alpha-particle RBE, even taking into account the sampling errors in the various epidemiological studies. The Mayak study is ongoing, with significant improvements in the dosimetry still to be made; the LSS risk estimates are also somewhat suspect, especially their dependence on gender and age at exposure (see Section II.G). In particular, it appears strange that the risk is higher in females than males among the A-bomb survivors, despite the much lower lung cancer incidence among Japanese women than men. Also, the BEIR VII lung cancer model reflects the negative trend with age at exposure obtained from the analysis of ***all solid tumors***, but there are still very little data to directly support a higher ***lung cancer*** risk for childhood exposures.

3. Summary and recommendations

Information on alpha-particle RBE_M (relative to γ-irradiation) for induction of cancer is sketchy, especially in humans. Laboratory studies are mostly indicative of a

value of about 20, but with likely variability depending on cancer site and animal species or strain. There is also evidence in both animals and humans that the RBE_M is much lower for induction of leukemia. Comparisons of data on lung cancer induction by inhaled radon progeny or plutonium with data on the A-bomb survivors yields somewhat conflicting results, suggesting possible errors in the data or in underlying assumptions regarding the form of the models, internal dosimetry, or the sensitivity of different parts of the lung. At this point, comparisons between the radon data and the LSS data suggest an RBE much lower than 20 for lung cancer induction, but the Mayak results so far fail to substantiate this. Further follow-up of the LSS cohort and additional information on the Mayak workers may help to resolve this issue.

At this time, we would propose multiplying site-specific gamma ray risk estimates by an RBE of 20 in order to derive corresponding estimates of risk from alpha radiation, with two exceptions: (1) an RBE = 1-3 for leukemia induced by alpha-emitters deposited in bone (EPA 1992) and (2) continued use of models derived from BEIR VI to estimate lung cancer risk from inhaled radon progeny (NAS 1999, EPA 2002). The low dose, γ-ray risk estimate for bone cancer would be obtained by dividing by 20 the risk per Gy estimated from patients injected with ^{224}Ra.

This approach is consistent with current EPA practice except in the case of breast cancer, where previously an RBE of 10 was employed rather than 20. The justification for the lower RBE was that the estimated (γ ray) DDREF was 1 for breast cancer but 2 for other solid tumors. The evidence for such a difference in DDREF appears weaker now, and, for simplicity we would propose using the same nominal DDREF (1.5) and RBE (20) for all solid tumors, including breast.

For all cancers except leukemia, EPA previously assigned a lognormal uncertainty distribution to the alpha-particle RBE, with a 90% CI from 5 to 40. The median value is thus about 14 (EPA 1999a). This distribution still seems reasonable to us. The uncertainty distribution for leukemia induced by alpha-emitters deposited in the bone was previously taken to be uniform over the interval [0,1] (EPA 1999a). Recent analyses of Thorotrast patient would suggest that this distribution be extended upward.

B. Lower Energy Beta Particles and Photons

As energetic electrons lose energy in passing through matter, they become more densely ionizing: i.e., the average distance between ionization events shrinks, and more energy is deposited in ionization clusters. As discussed earlier, such clusters can lead to DSBs and complex DNA damage that is more difficult for the cell to repair. Indeed it has been suggested that a large fraction of the residual damage caused by low-LET radiation may stem from these clusters produced at the ends of electron tracks. For this reason, it might also be expected that lower energy beta particles would be more biologically damaging than higher energy betas. Furthermore, since the energy distribution of secondary (Compton) electrons is shifted downward as incident photon energy is reduced, the biological effectiveness of photons might also be expected to rise with decreasing energy, implying that x rays might be more damaging than γ rays.

Results from many studies tend to confirm these predictions for low-LET radiations, including measurements of chromosome aberrations, mutations, cell transformation and cancer induction. The most direct source of data on the subject consists of comparative studies of x and γ ray induction of dicentrics in human lymphocytes. In these studies, 220-250 kVp x rays generally produced 2-3 times as many dicentrics as ^{60}Co gamma rays (NCRP 1990). The relevance of such measurements for cancer induction is unclear, however, since a dicentric will render a cell incapable of cell division. Other laboratory studies directed at ascertaining the RBE for various types of radiation relative to x rays or γ rays provide additional indirect information, suggesting again that x rays may be a factor of 2-3 times more hazardous than γ rays (Kocher et al. 2005, NCRP 1990, NRC 2006). Kocher et al. also conclude that x rays below 30 keV may have a slightly higher RBE than those in the range 30-250 keV.

Kocher et al. also consider what REFs should be applied to beta particles. They note that the average energy of a Compton electron produced by an incident 250 keV photon is 60 keV. It follows that beta particles above 60 keV should have the same RBE as photons above 250 keV: i.e., 1.0. The only radionuclide that emits a substantial fraction of its decay energy in the form of lower energy beta is ^{3}H, for which the mean beta energy is 5.7 keV. For ^{3}H betas, the authors recommend a lognormal uncertainty distribution with GM=2.4 and a GSD=1.4, corresponding to a 95% CI of (1.2, 5.0). The reference radiation is again chronic γ rays. This range is comparable to what was recommended for <30 keV photons and is generally consistent with experiments in which investigators compared ^{3}H with γ rays in the induction of various end-points.

No firm conclusions can be drawn from human epidemiological data. Risk coefficients derived from studies of cohorts medically irradiated with x rays are generally lower than what has been observed for the A-bomb survivors. Nevertheless, given the various uncertainties, such as those relating to dosimetry, sampling error, and possible confounders, it is still possible that medical x rays are significantly more carcinogenic, per unit dose, than γ rays. Based on the available evidence, it would appear reasonable to assign an RBE of 2 for most medical x rays and an RBE of 2.5, both for x rays below 30 keV and for ^{3}H beta particles.

IV. Risks from Prenatal Exposures

Currently, EPA does not include radiogenic cancers induced *in utero* as part of its population risk estimate. Although this contribution is expected to represent a small fraction of the total population risk, it is of particular concern because of the potentially higher radiation sensitivity in the embryo/fetus, and the evidence for an appreciably higher risk of radiogenic childhood cancers than that obtained with postnatal childhood exposures.

First carried out by Stewart and coworkers (1958), case-control studies of childhood cancer have shown a statistically significant association with diagnostic x rays *in utero*. The risk estimate derived from the Stewarts' "Oxford survey" is about 0.06 per Gy (95% C.I. 0.01-0.126) for all cancers and about 0.025 per Gy for leukemia (Mole 1990, Doll and Wakeford 1997). The LSS cohort results show no statistically significant excess of childhood cancers, on the other hand, and the upper bound estimate of the leukemia risk (Doll and Wakeford 1997).

This discrepancy has led to considerable controversy. The review article by Doll and Wakeford (1997) carefully considered many of the issues involved and concluded that the elevated risk in the fetus is probably real. They recommend the numerical risk estimates from the Oxford survey cited in the paragraph above. ICRP has recommended the value 6×10^{-2} Gy^{-1} for risk of a radiogenic cancer before the age of 14 from *in utero* x rays (ICRP 2000), and NCRP cites a value of 5×10^{-2} Sv^{-1} for fetal exposure to internally deposited radionuclides (NCRP 1998).

One possible contributing factor to the discrepancy between the Oxford survey and LSS data is the difference in type of radiation: x rays and gamma rays, respectively. As discussed in another section, for a fixed absorbed dose, the former may be about twice as effective in causing cancer. Based on this consideration, EPA proposes here a numerical risk estimate of 6×10^{-2} Gy^{-1} for x rays, but 3×10^{-2} Gy^{-1} for gamma rays and beta particles (other than from ^{3}H). Survival rates for childhood cancer in the U.S. are approximately 70-80% for both leukemia and solid tumors (SEER 2006c, Tables XXVIII-10 and XXIX-6), but this does not include delayed mortality resulting from second cancers arising from the treatment. In the Oxford study, roughly the same ERR/Gy was observed for solid tumor incidence as for leukemia. It is then reasonable to expect that approximately 20-30% of the radiation-induced cases would also be fatal.

Epidemiological follow-up of the atomic bomb survivors has indicated that individuals irradiated in utero have a risk similar to that of irradiated young children (Delongchamp et al. 1997). Based on this finding, we propose to adopt the same set of models employed for calculating risk for exposure to young children to assess the risk of adult cancers caused by *in utero* exposure.

V. Skin Cancer Risk

Current EPA risk estimates for radiation-induced skin cancer mortality (EPA 1994) are taken from ICRP Publication 59 (ICRP 1991). The one modification made by EPA was to apply a DDREF of 2 at low doses and dose rates. Recognizing that the great majority of nonmelanoma skin cancers are not life threatening or seriously disfiguring, EPA included only the fatal skin cancer cases in its estimates of cancer incidence risk. The contribution of skin cancers to the radiogenic risk from whole-body irradiation is then minor: about 0.2% and 0.13% of the total mortality and incidence, respectively.

ICRP's calculation of skin cancer incidence risk employed an ERR of 55% per Sv, along with U.S. baseline skin cancer incidence rates from the 1970's. The ICRP mortality estimate was also based on conservative assumptions that: (1) 1/6 of radiogenic skin cancers would be squamous cell carcinomas (SCC), the remainder basal cell carcinomas (BCC); (2) essentially all of the BCC would be curable, whereas about 1% of SCC would be fatal. Predicated on these considerations, ICRP Publication 59 estimated that 0.2% of the cases would be fatal.

The ICRP risk estimates closely mirror those previously published by Dr. Roy Shore (1990), who also served as a member of the committee that drafted ICRP Publication 59. Shore (2001) reviewed the subject again in light of additional information and concluded that essentially all of the radiation-induced skin cancers at low to moderate doses would be BCC. He maintains that the fatality rate for BCC is "virtually nil" but cites a study indicating a rate of 0.05% Weinstock (1994). Shore also notes that there is no persuasive evidence that radiation-induced BCC would be more fatal than sporadic cases.

At the same time, there is evidence that the baseline rates for BCC have increased dramatically since the 1970s, which might also result in a higher (absolute) risk per unit dose of inducing a radiogenic skin cancer.

It should be possible for EPA to estimate radiogenic skin cancer incidence and mortality using the ICRP risk model, but with a revised estimate of lethality for such cancers. Assuming that radiogenic skin cancers induced by low level ionizing radiation are all BCC, the fraction of cases expected to be fatal should be reduced, perhaps from 0.2% to 0.05%. An updated calculation with the ICRP relative risk model would further require recent information on baseline BCC incidence rates, which have increased dramatically over the last 3 decades (Karagas et al. 1999). SEER does not include nonmelanoma skin cancers in its data base, but statistics exist on the number of new cases each year. Together with assumptions on the variation of BCC incidence by age, it is anticipated that an approximate table of age-specific incidence rates could be derived.

VI. Thyroid Cancer Risk

The BEIR VII Report presents a model for estimating radiogenic thyroid cancer incidence based on a combined analysis of seven studies of individuals receiving external radiation (Ron et al. 1995). All seven studies were used to assess: the shape of the dose-response relationship; the effect of gender; the influence of age at exposure; temporal patterns of risk at times after exposure; the effects of fractionation; and the influence of screening and clinical surveillance on risk estimates (Ron et al. 1995). A pooled analysis of five of these studies was conducted to arrive at an excess ERR coefficient of 7.7/Gy for exposures under the age of 15.

BEIR VII adopts a simplified model in which the ERR depends only on whether the exposure occurred before age 30, but not on attained age or time since exposure. Based on the findings of Ron et al., BEIR VII also assigns twice the ERR to females as males. Given the higher baseline thyroid cancer rate in females (and their longer life expectancy) this translates into a radiogenic thyroid cancer risk that is five times higher for females than males. BEIR VII provides no estimate of the fraction of radiogenic cancers that would be fatal. It also does not deal with the issue of thyroid irradiation by internal emitters, including the important case of ^{131}I.

We also have available a preliminary draft of an EPA sponsored report from NCRP on thyroid radiation risk (T. Tenforde, private communication). This report presents several alternative risk models based primarily on the pooled analysis of Ron et al. The recommended model in the draft report differs in some ways from that in BEIR VII: (1) the dependence of ERR on age at exposure is more complex, falling off to zero by age 30; (2) the ERR peaks after 15 y and then falls off continuously with time since exposure; (3) the ERR/Gy is assumed to be equal for males and females. The net effect of these differences is that the population risk projection in the NCRP report is about 40% lower than that in BEIR VII.

Based on SEER data, the NCRP estimates that 5-7% of the radiogenic cancers would be fatal, and recommends adopting 7%. Our preliminary examination of the most recent SEER data suggests that the lethality is probably lower, perhaps 3-5%.

NCRP assigns an "RBE" of 0.6 to ^{131}I radiation relative to external x ray or gamma ray exposure. This is meant to include both the effects of dose fractionation (DDREF) and non-uniform dose distribution within the thyroid for ^{131}I.

The higher ERR for females cited in BEIR VII was derived from the pooled analysis, but the results from the individual studies were highly variable in this regard, and the gender difference was not statistically significant. NCRP's treatment of age and temporal dependence is more detailed. Overall, we now favor adoption of the NCRP thyroid cancer model, assuming that we would have a proper reference that can be cited. The mortality risk can be projected from either the NCRP or BEIR VII incidence model, using SEER data to estimate the fraction of radiogenic thyroid cancers that are fatal.

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