ESTIMATING RADIOGENIC CANCER RISKS

ADDENDUM: UNCERTAINTY ANALYSIS

May 1999

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May 1999

U.S. Environmental Protection Agency
1200 Penn. Ave. N.W. [updated address]
Washington, DC 20460

PREFACE

In November 1997, a draft version of this report (dated October 1997) was submitted by the Office of Radiation and Indoor Air (ORIA) to EPA's Science Advisory Board (SAB) for review. As part of the review, the Uncertainty in Radiogenic Cancer Risk Subcommittee (URRS) of the SAB's Radiation Advisory Committee (RAC) held two public meetings in Washington, DC, on November 20, 1997 and March 4, 1998 to receive briefings from ORIA staff and interested members of the public and to discuss the relevant issues. The SAB's report (EPA-SAB-RAC-99-008) was transmitted on February 18, 1999, to EPA Administrator, Carol Browner, with a cover letter signed by: Dr. Joan M. Daisey, Chair of the SAB; Dr. Stephen L. Brown, Chair of the RAC; and Dr. F. Owen Hoffman, Chair of the URRS. The SAB approved ORIA's approach to estimating uncertainty but suggested a number of possible improvements in the ORIA document or, in some cases, in future assessments of uncertainties. EPA responded to the issues raised in an April 29 letter from Robert Perciasepe, Assistant Administrator, Office of Air and Radiation to Dr. Daisey and made a number of changes in the final document to address SAB concerns.

This report was prepared by EPA staff members, Jerome S. Puskin, Christopher B. Nelson, and David J. Pawel, Office of Radiation and Indoor Air (ORIA), Criteria and Standards Division (CSD). The authors gratefully acknowledge the thoughtful comments received during the review process from the members of the URRS, F.O. Hoffman, S.L. Brown, W. Bair, P.G. Groer, D.G. Hoel, E. Mangione, L.E. Peterson, W.J. Schull, S.L. Simon, and A.C. Upton, as well as from additional reviewers, W.K. Sinclair, S. Jablon, C.E. Land, D.A. Pierce, and S.S. Yaniv. We also wish to thank Jonas Geduldig for developing the computer program, "Murky Ball," which was used to perform many of the Monte Carlo calculations in the development of this report.

The mailing address for the authors is:

U.S. Environmental Protection Agency
Office of Radiation and Indoor Air (6608J)
Washington, DC 20460

ABSTRACT

In 1994, EPA published a report entitled *Estimating Radiogenic Cancer Risks* (EPA 402-R-93-076), which described the Agency's methodology for deriving estimates of excess cancer morbidity and mortality due to low doses of ionizing radiation. Using this methodology, numerical estimates of the risk per unit dose were derived for each applicable cancer site, and for both low-LET and alpha-particle radiation. Subsequently, small adjustments were made to the procedure used in the 1994 document, chiefly the use of more recent vital statistics. These adjustments produced a slight increase in the estimated average risk from uniform, whole-body radiation: the low-LET nominal estimate increased from 5.1×10^{-2} Gy^{-1} to 5.75×10^{-2} Gy^{-1}. In this document, a method is described for estimating the uncertainties in the EPA risk projections. The uncertainty in each site-specific (or whole-body) risk estimate is treated as the product of several independent sources of uncertainty, *e.g.*, sampling errors in the epidemiologic data underlying the risk model, or uncertainty in the extrapolation of observations at high acute doses to chronic low dose conditions. A distribution is assigned to each source of uncertainty, which defines the probability that the assumption employed in EPA's risk model with respect to this source of uncertainty either underestimates or overestimates the risk by any specified amount. The joint probability distribution for the uncertainty due to all sources combined is then calculated using Monte Carlo techniques. A detailed uncertainty analysis is performed for the risks from uniform, low-LET irradiation of the whole body, the lung, and the bone marrow. For the whole body or the bone marrow, the upper limit on the 90% confidence interval is about 2 times higher, and the lower limit is about 3 times lower, than the respective nominal risk estimate. In the case of the lung, the upper bound is also about a factor of 2 higher, but the lower bound is about a factor of 5 times lower, than the nominal estimate.

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I. Introduction

In 1994, EPA published *Estimating Radiogenic Cancer Risks* ("EPA94"), which described the Agency's methodology for calculating excess cancer morbidity and mortality risks due to ionizing radiation (EPA 1994). For most cancer sites, a "GMC model" was employed in which each age-, sex- and site-specific relative risk coefficient was obtained by taking a geometric mean of the corresponding coefficients in the "multiplicative" and "NIH" projection models derived from Japanese A-bomb survivors Lifespan Study (LSS) data. Subsequently, the risk projections in EPA94 were updated in light of more recent (1990) U.S. Vital Statistics (EPA 1997). In this document, a methodology is developed for estimating the uncertainties in the EPA risk projections. Using that methodology, quantitative estimates of uncertainty in cancer mortality risk estimates are derived for low dose, low-LET exposures to the whole body, the lung, and the bone marrow.

II. Update of Risk Estimates

In 1997, EPA issued *Federal Guidance Report No. 13, Interim Version* (FGR 13), which provides risk estimates for chronic, low level exposures to over 150 radionuclides through a number of pathways (internal exposure through ingestion or inhalation, external exposure from surface and soil contamination or from submersion) (EPA 1997). [The final version of FGR 13 is expected to be published in 1999.] The methodology in FGR 13 differs from that in EPA94 in two main respects: (1) the use of newly recommended ICRP age-specific dosimetry models and (2) the substitution of 1990 for 1980 U.S. Vital Statistics. The discussion here focuses on the site-specific risks per unit dose; for this purpose, only the latter of these changes is relevant.

In EPA94, 1980 U.S. baseline cancer mortality rates were used to: (1) derive the relative risk coefficients for the NIH/GMC projection models and (2) project risk in the U.S. population based on the site-specific relative risk coefficients. In FGR 13, baseline cancer rates for these purposes were obtained from the 1990 U.S. Vital Statistics. In addition, EPA's methodology for projecting risk utilizes a survival function, which gives the probability that a person in the population will survive to any specified age. In FGR 13 calculations, the survival function was also updated to reflect 1990 Vital Statistics. For consistency, other minor changes were made to the risk model in FGR 13 (EPA 1997).

Table 1 lists the revised site-specific risk estimates presented in FGR 13. The previous EPA94 values, calculated using 1980 Vital Statistics, are shown for comparison. For the most part, the changes are minimal. In particular, the estimated cancer mortality risk associated with uniform whole-body irradiation has increased only slightly, from 5.09×10^{-2} per Gy to 5.75×10^{-2} per Gy. The most notable change appears in the lung cancer risk, reflecting an increase in the baseline rate between 1980 and

1990. [Use of the 1990 Vital Statistics also changes cancer incidence risk estimates slightly, the whole-body morbidity risk increasing from 7.60×10^{-2} to 8.46×10^{-2} per Gy.]

TABLE 1

EPA low dose, low dose rate cancer mortality risk estimates (10^{-4} per Gy)

Cancer Site	EPA 1994	FGR 13
Esophagus	9.0	11.7
Stomach	44.4	40.7
Colon	98.2	104.2
Liver	15.0	15.0
Lung	71.6	98.8
Bone	0.9	0.9
Skin	1.0	1.0
Breast	46.2	50.6
Ovary	16.6	14.9
Bladder	24.9	23.8
Kidney	5.5	5.1
Thyroid	3.2	3.2
Leukemia	49.6	55.7
Remainder	123.1	149.5
TOTAL	509.1	575.2

III. Uncertainty Analysis

An analysis of the uncertainties in the fatal cancer risk estimate for uniform whole-body, low-LET radiation has been published by the NCRP in its Report No. 126 (NCRP 1996). Based on its analysis, the NCRP committee arrived at an uncertainty range of 1.5×10^{-2}/Gy to 8.2×10^{-2}/Gy. In some respects, the analysis and results for whole-body, low-LET radiation here closely parallels that in NCRP No. 126. However, we expand the framework to include estimation of uncertainties in specific organ risks, and to include high-LET as well as low-LET radiation. A detailed analysis is provided for lung cancer and leukemia. For other sites, probability distributions are indicated for some sources of uncertainty, but additional analysis would be required to arrive at quantitative uncertainty bounds on the risk coefficient. Coupled with estimates of uncertainty in organ doses resulting from the intake of internally deposited radionuclides, these estimates of uncertainty in organ-specific risk per unit dose could

be used to calculate uncertainties in the risks from ingested or inhaled radionuclides. However, in summing the organ-specific contributions, careful attention must be given to possible correlations in the uncertainties for the various sites.

To quantify the uncertainties associated with the risk estimates derived here primarily from the LSS, a methodology similar to that previously employed for assessing the uncertainties in radon risk can be applied (Puskin 1992). First, in a manner similar to that described by Sinclair (1993), the uncertainty in each site specific risk estimate is treated mathematically as the product of several independent sources of uncertainty, including: sampling variations, errors in dosimetry, and errors in medical ascertainment with respect to the epidemiological data; the modeling of the dependence of risk on age at exposure and time since exposure; the transport of risk estimates from the study population to the U.S. population; the extrapolation to low doses and dose rates; and, for high-LET radiation, uncertainty in RBE. Second, a distribution is assigned to each source of uncertainty, which defines the probability that the assumption employed in the model pertaining to this source of uncertainty either underestimates or overestimates the risk by any specified amount. Finally, the joint probability distribution for the combined uncertainty due to all sources is calculated analytically as was done for radon or, as here, with the aid of Monte Carlo techniques.

Necessarily, subjective judgment is usually required in assigning “probability” distributions. Where this is the case, the uncertainty will be characterized as a "subjective confidence interval" rather than as a "confidence interval." [The term "credibility interval" has also been used for this purpose (NIH 1985).]

A. Sampling Variability

For the statistical analysis of the LSS data, the deaths and person-years of survival for the 75,991 individuals in the DS86 subcohort were aggregated by city, sex, 6 age (at time of bomb) categories, 7 follow-up intervals, and 10 radiation dose intervals (Shimizu *et al.* 1990). Site-specific risk coefficients were calculated with a maximum likelihood estimation method, which assumes that the number of deaths in each group are independent Poisson variates.

Based on this analysis, Shimizu *et al.* have derived excess relative risk estimates, with associated 90% confidence intervals, for a number of sites. These are listed in Table 2. It can be seen that, for most sites, the upper and lower confidence interval limits, U and L, respectively, are distributed nearly symmetrically about the central estimate of the risk coefficient, as one would expect if the errors are distributed normally about this value. [The more skewed distributions occur for organs such as esophagus and ovary, which would ordinarily contribute only a small proportion of the total risk from a given exposure.] Hence, for each site, i, we shall represent the uncertainty due to sampling variation as a normal distribution with mean $(U_i+L_i)/2$ and

standard deviation $(U_i-L_i)/3.29$. This distribution, in general, has a mean displaced slightly (upward) from the maximum likelihood estimate but with the same 90% confidence interval limits obtained from the statistical analysis of the data.

TABLE 2

Uncertainties due to sampling variations in the LSS

Cancer Site	Excess Relative Risk per Gy[a]	Derived Distribution Mean (s.d.)[b]
Leukemia	5.21 (3.83, 7.12)	5.48 (1.00)
All cancers except leukemia	0.41 (0.32, 0.51)	0.42 (0.06)
Esophagus	0.58 (0.13, 1.24)	0.69 (0.34)
Stomach	0.27 (0.14, 0.43)	0.29 (0.09)
Colon	0.85 (0.39, 1.45)	0.92 (0.32)
Lung	0.63 (0.35, 0.97)	0.66 (0.19)
Female breast[c]	1.19 (0.56, 2.09)	1.33 (0.47)
Ovary	1.33 (0.37, 2.86)	1.62 (0.76)
Urinary tract	1.27 (0.53, 2.37)	1.45 (0.56)

[a] Relative risk coefficient and 90% confidence interval from Shimizu *et al.* (1990).
[b] Mean and standard deviation of normal distribution used to characterize the uncertainty in the relative risk coefficient (see text).
[c] Included here for completeness. EPA's breast cancer risk estimate is based on data collected on medically irradiated North American women (EPA94: Section IV).

The uncertainties listed in Table 2 reflect the uncertainties in the age-averaged relative risk coefficient determined over the period of epidemiologic follow-up. The percent error in the coefficient applicable to any particular age-at-exposure group is highly variable. Since those exposed as children have just entered their cancer prone years, sampling uncertainties are particularly high for these survivors, who so far show the highest excess relative risks per Gy. Consequently, when risks are projected over a lifetime and summed across age groups to obtain population risks, the uncertainty due to sampling error may be considerably larger than indicated. The magnitude of this uncertainty will depend, in part, on how much each age-at-exposure group contributes

to the lifetime risk, which in turn depends on the detailed characteristics of the age and temporal projection model (see below). Thus, the uncertainties due to sampling variations and due to temporal modeling are not really independent as assumed here. A comprehensive assessment of these two sources of uncertainty would require an extensive reanalysis of the LSS data.

B. Diagnostic Misclassification

Two types of diagnostic misclassification of cancer can occur: classification of cancers as noncancers (detection error) and erroneous classification of non-cancer cases as cancer (confirmation error). The former leads to an underestimate of the excess absolute risk (EAR), but does not affect the estimated excess relative risk (ERR). Conversely, the latter leads to an underestimate of the ERR but does not affect the EAR (NCRP 1997).

Based on results from an RERF autopsy study, Sposto *et al.* (1992) estimated that, due to diagnostic misclassification between cancer and noncancer causes of death, the estimated ERR of induced cancers in the LSS population should be corrected upward by a factor of 1.13. Using information in Sposto *et al.*, but two different calculational procedures, the NCRP 126 Committee found that the 90% confidence range for the correction factor to the ERR due to confirmation error is 1.09-1.18, or 1.095-1.156. However, for the purposes of its uncertainty analysis, the Committee assigned a probability distribution N(1.1,0.05), which translates into a 90% subjective confidence interval from 1.02 to 1.18.

For most solid tumors, EPA's risk model (GMC model) coefficients were obtained by a geometric averaging of the corresponding relative risk coefficients for the multiplicative and NIH projection models. The correction factor of 1.13 is appropriate for the multiplicative but not the NIH model, even though the latter is also a relative risk model. However, the NIH model is constructed in such a way that it projects approximately the same *absolute* risk in the U.S. population (over a 40-y period after exposure) as observed in the LSS. For this reason, the correction for misclassification in the NIH model should be the same as for the EAR rather than the ERR estimates. Based on the approach outlined by Sposto *et al.* (1992), Pierce *et al. (1996)* estimate that the EAR should be adjusted upward by about 16% to reflect errors in diagnostic misclassification.

In view of the information above, we estimate that the EPA projection of the risk from whole-body irradiation should be increased by about 15% to adjust for misclassification error. We have assigned a normal probability distribution, N(1.15,0.06), to the correction factor for misclassification, corresponding to a 90% subjective confidence interval from 1.05-1.25. Misclassification errors vary considerably by cancer site, both with respect to proper identification of cancer as the

cause of death and with respect to the primary site. Consequently, the assignment of an uncertainty distribution associated with diagnostic misclassification should be readdressed in the case of nonuniform irradiation.

C. Temporal Dependence

A substantial fraction of the estimated population risk is associated with childhood exposures. As discussed in EPA94 (Section II.B), there is considerable uncertainty in the estimated risk from doses received by children. First, statistical uncertainties in the age-specific risk coefficients are generally large, especially for the youngest age groups among the A-bomb survivors, since those individuals are now just entering the years of life in which cancers are commonly expressed. Second, there is suggestive evidence that for some types of solid tumors the excess relative risk due to childhood exposures may decrease over time (Little *et al.* 1991).

With respect to adult exposures, a temporal fall-off in the excess relative risk of lung cancer has been observed in radon-exposed underground miners (NAS 1988) and in irradiated spondylitic patients (Darby *et al.* 1987), but there is no clear indication of such a fall-off in the A-bomb survivors who were over age 20 at the time of the bomb (Little and Charles 1989). For childhood exposures, Little *et al.* (1991) have concluded that there is evidence of a temporal fall-off. Based on an analysis of observed temporal trends in risk among 4 cohorts of children exposed to radiation, including those from the LSS, they estimate that the lifetime risk for solid tumors in the (UK) population may be 30-45% lower than projected by the constant relative risk model.

In developing its estimate of uncertainty in lifetime risk associated with temporal projection, NCRP Report No. 126 notes that a model in which the excess relative risk per Sv depends only on attained age appears to fit the LSS cancer mortality data as well as a model in which the relative risk depends only on the age at exposure (but see Little *et al.* 1997). The former model, proposed by Kellerer and Barclay (1992), projects about a factor of 2 lower risk. Noting also that there is some possibility that the relative risk may actually increase with age, the Committee suggested a triangular distribution of uncertainty with a most likely value of 1.00 and a range from 0.50 to 1.10.

In assigning uncertainties associated with temporal projection, three classes of cancer sites should be considered:

(1) sites for which follow-up is essentially complete, with relatively few additional radiation induced cancers expected past the present period of epidemiological follow-up. For this group, which might include bone sarcomas and leukemia, the uncertainty in lifetime risk associated with temporal projection outside the period of follow-up would be small (however, see Section J.2).

(2) sites for which a constant relative risk model has been used to project risk beyond the period of follow-up, but for which the risk coefficients are dependent on the age at exposure. This group includes stomach, colon, lung, breast, thyroid, and remainder sites. Most of the projected lifetime risk for these sites is associated with exposures before age 20. As discussed above, the contribution of childhood exposures is highly uncertain in view of the statistical limitations and possible decreases in relative risk with time after exposure. For this group of sites, the model appears more likely to overestimate than to underestimate the population risk. We assign a range of 0.5-1.0 to the uncertainty factor associated with age and temporal dependence for each of these sites except the colon. For colon, a large fraction of the estimated population risk is from childhood exposures, but the childhood risk is based on a very limited number of observed cancers; hence, for this organ, we assign a larger range of uncertainty, 0.4-1.0.

For any individual site, the distribution of uncertainty is assumed to be uniform on an arithmetic scale; *e.g.*, in the case of the colon, it is assumed that if we consider only the uncertainty in time projection, the nominal risk estimate should be multiplied by a factor of x, where x is a random variable uniformly distributed in (0.4,1).

(3) sites for which a constant relative risk projection has been used, but for which the risk coefficient reflects a single age-averaged value. This group includes esophagus, liver, bladder, kidney, ovary, and skin. The data available on these sites are generally sketchy and heavily weighted towards adult exposures. It is plausible that childhood exposures may convey a higher risk than adult exposures for these sites, as they appear to do for other sites. Consequently, the model used to project risk, in this case, may tend to understate the population risk. Typically, the relative risks for childhood exposures are found to be 2 to 3 times the average for adults (Shimizu *et al.* 1990). If risks for childhood exposures are similarly elevated for the sites in question, the population risks would be increased by roughly 50%. On the other hand, some fall-off in relative risk may occur for these sites even in the case of adult exposures. An uncertainty factor between 0.8 and 1.5 is judged to be reasonable for these sites; the factor is again assumed to be distributed uniformly within this interval (on an arithmetic scale).

D. Transport of Risk Estimates from Japanese A-Bomb Survivors

As discussed in Sections II and IV of EPA94, uncertainty exists over how to apply the results of the analysis of the Japanese A-bomb survivors to the estimation of risk in the US population, particularly for cancer sites which exhibit markedly different baseline rates in the two populations. Reflecting this uncertainty, EPA has adopted a model for most sites in which the age- and sex-specific risk coefficients are a geometric mean of the corresponding coefficients used in the multiplicative and NIH projection models. In transporting risk across populations, the multiplicative model presumes that

the excess risk will scale with the baseline cancer rate, whereas the NIH model presumes that the excess risk is nearly independent of differences in the baseline rate. Viewed from a mechanistic standpoint, the former presumes that radiation risks act multiplicatively with the other risks for cancer, while the latter presumes that the interaction is roughly additive.

For those organs where the GMC model has been employed to calculate risk, the NIH and multiplicative projections will be used as uncertainty bounds on the component of uncertainty associated with transporting the risk. In view of the lack of information on how radiation interacts with other factors affecting carcinogenesis, the distribution between these two bounds is taken to be uniform on a logarithmic scale. [The "loguniform" distribution has the property that the probability of finding the random variable in a small interval dx is dx/x; thus, it is weighted more towards lower values than a distribution which is uniform over the same range on an arithmetic scale.]

It is not obvious how the uncertainties in specific organ risks associated with transport across populations should be combined in evaluating the uncertainty in risk due to an exposure to multiple organs. On one hand, the uncertainties in individual organ risks could be considered as independent; on the other, as perfectly correlated. In the former instance, the random variable defining the point on the distribution between the multiplicative and NIH model would be sampled independently for each site. In the latter, the same value of the random variable would be assigned to each site. For uniform, whole-body irradiation, the transport uncertainty does not contribute strongly to the uncertainty in total cancer risk (see Section H), and it makes little difference which of these methods is chosen. In the absence of information to the contrary, and for calculational convenience, the transport uncertainty will be taken to be independent of cancer site.

E. Errors in Dosimetry

Random errors in the individual dose estimates for the A-bomb survivor population have been estimated at 25-45% (Jablon 1971, Pierce *et al.* 1990, Pierce and Vaeth 1991). The net result of such errors is to overestimate the average dose in the high dose groups (Pierce and Vaeth 1991). As a result, for a linear fit to the data, the slope of the dose response will be biased low by roughly 10% (Pierce *et al.* 1990). More significantly, perhaps, the shape of the dose response will be distorted towards a convex (downward) curvature; hence, a true linear-quadratic dependence may be distorted to look linear (Pierce and Vaeth 1991). This possible distortion has been discussed in EPA94 (Section II.B.) and is factored into the subjective estimate of uncertainty in the DDREF presented in the next section.

Measurements of neutron activation products indicate that DS86 may seriously underestimate neutron doses for Hiroshima survivors, the relative magnitude of the

error increasing with distance from the epicenter (Straume *et al.* 1992). If neutron doses have been underestimated, then a larger fraction of the radiogenic cancers would be attributable to neutrons, and the estimated gamma ray risk would have to be reduced. Using the tentative revised estimates of neutron flux derived by Straume *et al.*, and assuming a neutron RBE of 20, Preston *et al.* (1993) have calculated that the gamma ray risk estimate for all cancers other than leukemia may be reduced by about 22%. Alternatively, if a neutron RBE of 10 is assumed, the estimated reduction in gamma ray risk is about 13%. Since the ratio of organ doses to kerma doses for both neutrons and gamma rays vary somewhat by organ, the magnitude of the estimated error would also vary by cancer site. Hence, for a nonuniform dose distribution, the appropriate correction may be larger or smaller than the average value calculated by Preston *et al.*

NCRP Report No. 126 identified two additional sources of uncertainty relating to the DS86 dosimetry: bias in gamma ray estimates and uncertainty in neutron RBE. Thus, altogether, the Committee analyzed four distinct sources of error relating to DS86 dosimetry, which they took to be uncorrelated. An uncertainty distribution was ascribed to each of the four sources of error, as summarized in Table 3.

TABLE 3

Dosimetric uncertainties

Parameter	Symbol	Parameter Value at Peak	Distribution	Range* or 90% CI**
Random errors	$f(R_E)$	1.1	Normal	1.0 to 1.2
Neutron weight	$f(N_R)$	1.0	Triangular	0.9 to 1.1
Neutron dose	$f(D_n)$	1.1	Triangular	1.0 to 1.3
Gamma-ray free field	$f(D_\gamma)$	1.1	Triangular	1.0 to 1.4

* Range of triangular distributions

** 90% confidence interval for the normal distribution

The combined distribution, f(D), representing the multiplicative uncertainty in risk due to all four sources of dosimetric uncertainty, was derived using Monte Carlo techniques and the equation below:

$$f(D) = \frac{f(R_E)}{f(D_\gamma) \times f(N_R) \times f(D_n)} \quad (1)$$

The resulting distribution f(D) is approximately normal with a mean of 0.84 and a 90% confidence interval from 0.69 to 1.0; the standard deviation of this normal distribution is about 0.095. The NCRP distribution for dosimetric uncertainty is adopted here for the analysis of the uncertainty in whole-body risk.

In estimating the error in risk associated with possible underestimation of the neutron dose Preston *et al.* used the colon dose as a surrogate for the whole-body dose. Transmission of neutrons to some organs is significantly higher than to the colon (see: NAS 1990, p. 195). For these organs, the relative error in the risk coefficient due to an underestimation of neutron dose would be increased (see Section J).

F. Low Dose (Low Dose Rate) Extrapolation

Radiogenic cancer risk estimates are primarily based on observed excess cancer deaths among A-bomb survivors receiving acute doses of 0.1 to 4 Gy. It would appear that epidemiology can provide no direct information on the very small risks that may arise from environmental exposures to radiation (~0.1 Gy/y). Risk estimates at low doses and dose rates are extrapolations based upon radiobiological data and our current theoretical understanding of radiation carcinogenesis. This extrapolation is usually the most important source of uncertainty in estimates of risk from environmental exposures to low-LET radiation. A detailed analysis of the issues involved in this extrapolation has been published by the United Nations (UNSCEAR 1993).

Carcinogenesis is understood to be a multistage process in which a single cell gives rise to a tumor, with mutation of DNA required in one or more of the steps leading to malignancy. Since cancer is a common disease, the background rates for each of these steps must be greater than zero, and any filtration mechanism for removing precancerous cells must be imperfect. Hence, any exposure that increases the rate of somatic mutations would be expected to have some risk of causing cancer. Traversal of a single ionizing track through a cell appears to be capable of causing DNA damage that cannot always be faithfully repaired. A dose threshold for radiation carcinogenesis is therefore unlikely.

Studies at the molecular, cellular, tissue, and whole-animal level have demonstrated that radiation damage increases with dose and that, at least for low-LET

radiation, it is often greater, per unit exposure, at high doses and dose rates than at low doses and dose rates. Qualitatively, this can be understood as a reduction in repair efficiency at the higher doses and dose rates, either due to induction of more complex damage or due to saturation of repair enzymes (Goodhead 1982). The reduction in effectiveness at low doses and dose rates, relative to that observed at high acute doses, is commonly expressed in terms of a dose and dose rate effectiveness factor (DDREF).

The damage from low-LET radiation at low and moderate doses is commonly modeled as a linear-quadratic (LQ) function of dose ($R= \alpha D + \beta \cdot D^2$). At low doses, the relationship reduces to a linear function of dose, and experiments on animals or mammalian cells generally indicate that the relative contribution of the quadratic term is negligible below about 0.2 Gy. In this domain, multi-track effects are presumed to be negligible, and, as a result, the response there is expected to be independent of dose rate. Supporting this picture are results of experiments showing an equivalence of the slope of the dose response observed at low doses with that observed when high doses are fractionated or delivered chronically (NCRP 1980); however, this equivalence does not seem to be universal (UNSCEAR 1993). There are compelling reasons to believe that the dose response for induction of mutations or cancer should be linear down in the dose range (<< 0.001 Gy) where multiple traversals of cell nuclei are rare. However, direct evidence from epidemiology or radiobiology below about 0.01 to 0.1 Gy is lacking. Consequently, without a fuller understanding of the mechanisms involved in radiation carcinogenesis, a significant deviation from linearity below 0.01 Gy cannot be categorically ruled out, even though the dose response derived from epidemiological data at higher doses appears to be fairly linear.

According to the LQ model, the linear component of the dose response is expected to be predictive of the risk at very low doses and dose rates. The DDREF, in this view, is obtained from the ratio of the slopes calculated using linear and LQ fits to the data, respectively. Under the assumption of a LQ dose response, the maximum likelihood estimate for the DDREF derived from the LSS data is about 2 for leukemia but only about 1 for solid tumors (Shimizu *et al.* 1990, NAS 1990). The upper bound on the DDREF is also higher for leukemia. If the possible distorting effects of errors in dosimetry (estimated to be roughly ±30%) are taken into account, the upper bound estimate (95% confidence bound) for the DDREF is about 5 for leukemia and about 3 for all other cancers combined (Pierce and Vaeth 1991). However, the analysis of Pierce and Vaeth did not consider all the potential errors in dosimetry, most notably, the possibly large underestimation of neutrons at Hiroshima discussed above. Such an error could have distorted the shape of the dose-response relationship for gamma rays (Kellerer and Nekolla 1997). If neutron fluxes were to be increased by as much as proposed by Straume (1992), then a DDREF as high as 10 might be consistent with the LSS data (D. Preston, unpublished results).

Studies of tumorigenesis in animals most often yield DDREFs in the range of 2 to 5 (NAS 1990). Thus, the DDREF derived from a dose-response fit to the LSS data on solid tumors is consistent with values near, or below, the lower end of the range derived from animal studies. There are very limited data on humans, however, which bear directly on the question of extrapolation to *low dose rates*. Data on medically irradiated cohorts indicate that fractionation of the dose has no large effect on the risk of radiogenic thyroid cancer or breast cancer (Shore *et al.* 1984, Davis *et al.* 1989, Howe 1992). On the other hand, the apparent absence of radiogenic lung cancers in fluoroscopy patients receiving fractionated doses of X-rays suggest that a larger DDREF may be applicable to the lung (Davis *et al.* 1989, Howe 1992). Although the authors claim that these findings are inconsistent with projections from the A-bomb survivors based on a low value for the DDREF, no detailed statistical analysis is provided from which one can infer a lower bound on the lung cancer DDREF. Such an analysis would have to address: (1) the sampling errors in both the LSS and fluoroscopy data; (2) the dependence of risk on age and sex; and (3) the differences in baseline lung cancer rates between the Japanese and North American populations. Finally, careful attention must be paid to the possible confounding influence of tuberculosis within the fluoroscopy cohorts.

There is evidence that low dose radiation may induce or activate cellular DNA repair mechanisms through a so-called “adaptive response,” leading to speculation that low doses may be protective against cancer (Feinendegen 1991). However, the effects seen to date have been essentially short term; for this reason, it does not yet appear likely that the *net* effect of the radiation would be beneficial (Puskin 1997). At this point, too little is known about this adaptive response to influence estimates of risk at low doses and dose rates. It is also theoretically possible that low dose radiation could stimulate other protective mechanisms, *e.g.,* programmed cell death (apoptosis). A detailed review of possible radiation induced adaptive responses can be found in the UNSCEAR 1994 report.

Assigning an uncertainty distribution to the DDREF requires subjective judgement. For all cancers combined, NCRP Report No. 126 posited a piecewise linear distribution, peaked at 2.0, and spanning the interval from 1 to 5. As a default for most sites, and for uniform whole-body irradiation, we have adopted a distribution that places somewhat more weight on a DDREF value close to 1 and assigns a finite probability to DDREFs > 5. The distribution is uniform from 1 to 2, falling off exponentially for values greater than 2. The two parts of the distribution are normalized so that: (1) the probability density function is continuous and (2) the integrals of the uniform and exponential portions are each 0.5. Mathematically, the probability density for the DDREF, f(x), can then be written:

$$f(x) = 0.5 \qquad 1 \le x \le 2 \qquad (2a)$$

$$f(x) = 0.5\, e^{-(x - 2)} \qquad x > 2 \qquad (2b)$$

The median (2.00) and mean (2.25) of this distribution are slightly lower than the corresponding values based on the NCRP distribution (2.34 and 2.48). The 90% subjective confidence interval (CI) is 1.10-4.30, compared to 1.25-4.13 for the NCRP distribution. The two distributions are compared in Figures 1a and 1b.

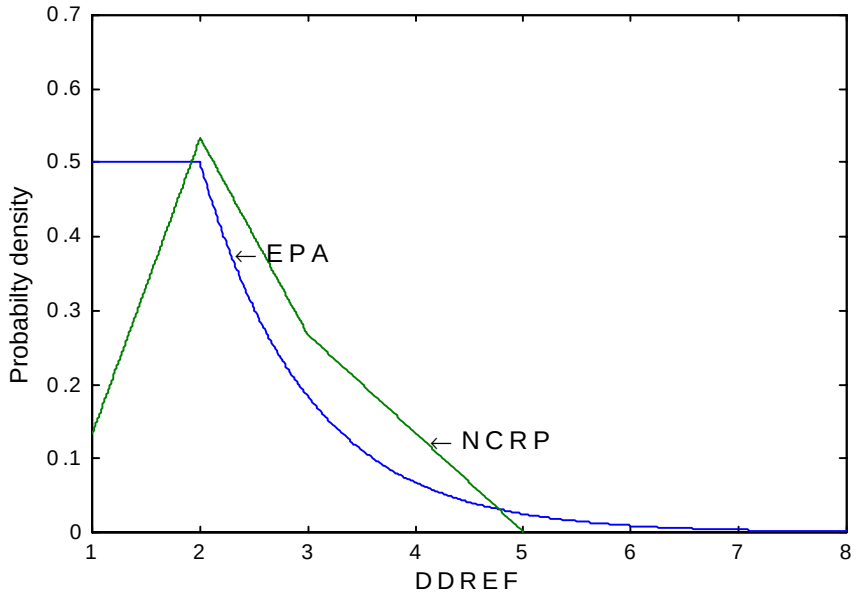

Figure 1a. DDREF uncertainty distributions.

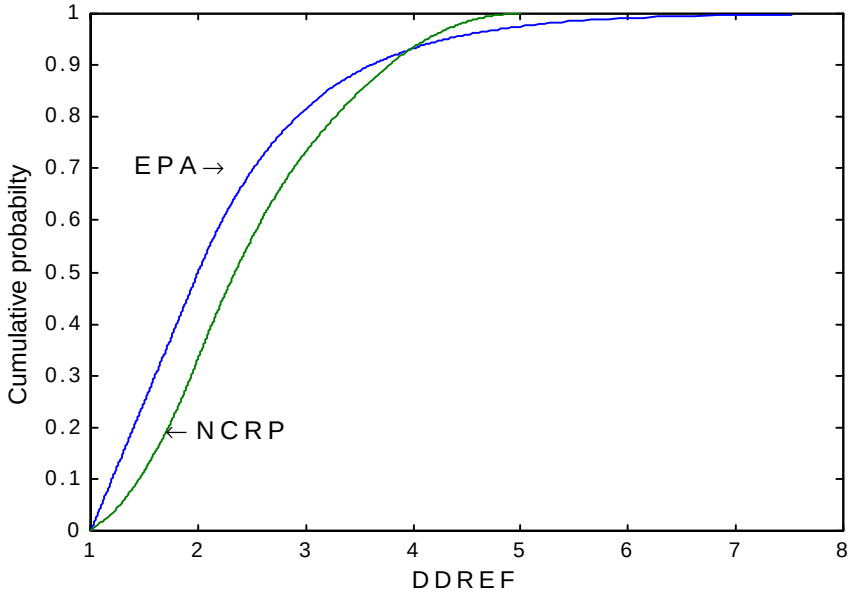

Figure 1b. Cumulative DDREF uncertainty distributions.

No probability is assigned here to a threshold or to a protective effect of low dose rate radiation. Likewise, no weight is given to the possibility of a heightened sensitivity at low doses (DDREF < 1). None of these alternatives is incompatible with the epidemiological data, which are generally not informative about risks at very low doses. Currently, support for these concepts from radiation biology is weak (UNSCEAR 1993, 1994). However, newly observed effects of ionizing radiation on cells, including the adaptive response (Olivieri *et al.* 1984, UNSCEAR 1994, Wolff 1996), genomic instability (Kennedy *et al.* 1980, Morgan *et al*. 1996) and the "bystander effect" (Nagasawa and Little 1992, Deshpande *et al.* 1996, Lorimore *et al.* 1998), could eventually lead to some fundamental revisions in the theory of radiation carcinogenesis and estimates of risk at low doses. Our present understanding of these phenomena is very limited, and any implications for low dose risk estimation are highly speculative (UNSCEAR 1993, 1994; Fry *et al.* 1998). Consequently, the reported observations on these effects did not influence our quantitative assessment of uncertainty.

Several reviewers of this report have recommended that, in view of what appears to be a linear dose response in the LSS data, we should assign a finite probability to a DDREF of exactly 1–at least for solid tumors. In our judgement, adequate weight is already placed on DDREF values near 1. For example, 12.5% of the total area is contained between DDREF values of 1 and 1.25: 2½ times that for the NCRP distribution. To further explore this issue, a Monte Carlo simulation was performed using a modified distribution for the DDREF, which assigned a 10% probability for a DDREF equal to 1, keeping the shape of the distribution otherwise constant. This modification produced about a 13% increase in the upper bound estimate of whole-body risk and about a 4% increase in the lower bound estimate (see Section H below). Thus, the uncertainty range for the risk is not very sensitive to inclusion of a small probability for a DDREF of 1.

It is quite likely that the DDREF varies from one cancer site to another, and for certain sites there may be enough information to justify an alternative probability distribution. For example, a narrower uncertainty range in the DDREF for breast cancer may be warranted in view of the linearity of the dose response observed in several study populations and the apparent invariance in risk with dose fractionation (Hrubec *et al.* 1989, NAS 1990, Howe 1992, Tokunaga *et al.* 1994). A modified uncertainty distribution may also be appropriate for leukemia, for which the dose response in the LSS appears to be concave upward. Other sites should perhaps be assigned different DDREF uncertainty distributions, as well. The assumption we are making here is that, for an essentially uniform dose to all target tissues, the overall uncertainty is dominated by the nominal distribution described above. A more careful consideration of the DDREF uncertainty distribution may be needed for cases where the dose is heavily concentrated in a few specific target tissues.

G. Alpha Particle RBE

The NCRP has recently reviewed the laboratory data bearing on the issue of RBEs for high-LET radiation (NCRP 1990). From an examination of the data on internal emitters, 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 RBE of alpha emitters tends to increase as the dose decreases, probably mainly due to the decreased effectiveness per Gy of low-LET radiation at low doses and low dose rates." Also relevant are the findings on external exposures to fission neutrons, which, because of their comparable LET, are expected to have an RBE similar to that for alpha particles. For neutrons, a wide range of RBE has been observed, but if one considers only the most relevant data on tumorigenesis, the range is about 6 to 60.

EPA is generally concerned with low dose, low dose rate conditions. Under these conditions, the low-LET risk is presumed to be reduced by a DDREF, and the alpha particle RBE is increased by this same factor. For solid tumors other than breast, EPA has adopted a nominal DDREF of 2 and an RBE of 20 (EPA 1994). [For the breast, these nominal values are 1 and 10, respectively (EPA 1994).] The DDREF adopted for solid tumors is somewhat lower than what is often observed in animal experiments. It follows that RBEs determined from low dose extrapolation of experimental data may be higher than what would apply to humans. Taking this consideration into account, for solid tumor induction, we assign to the RBE an uncertainty range of 5 to 40 (90% subjective confidence interval). [Stated another way, the risk per unit dose for alpha radiation is estimated to be 2.5-20 times higher than that for high acute doses of low-LET radiation.] Within this range the uncertainty is assumed to be distributed lognormally around the geometric mean of the upper and lower subjective confidence bounds.

Since there is a dearth of cancer sites for which there are detailed epidemiological data relating to both high- and low-LET exposures, one cannot generally base estimates of alpha particle RBE on human data. One apparent exception is leukemia. The risk of leukemia induced by internally deposited radium appears to be much lower than what one would calculate based on low-LET epidemiological data and an RBE of 20 (NAS 1988). Possibly, the discrepancy can be explained in terms of error in estimates of alpha particle dose to sensitive cells in the bone marrow. For purposes of our risk assessments, we have treated this as a special case, basing our high-LET leukemia risk estimates directly on high-LET epidemiological data (EPA 1994).

In calculating leukemia risk from alpha irradiation, EPA employs a nominal RBE of 1 (EPA 1994). Although experimental studies of neutron irradiated animals also point to a low RBE (about 2 or 3) for leukemia induction (Ullrich and Preston 1987), the

RBE of 1 was based primarily on epidemiological studies of patients injected with ^{232}Th (Thorotrast). In the Thorotrast studies, a clear excess of leukemia was observed, consistent with a risk estimate of roughly 50 leukemias per 10^4 person-Gy (Mays *et al.* 1985, NAS 1988). Numerically, this is about equal to the low-LET leukemia risk estimate derived from the LSS, assuming a DDREF of 2 (EPA 1995), thus implying an RBE of about 1.

Recently, some investigators have proposed a readjustment of the dosimetry in the Thorotrast studies, which would imply an upward revision of the leukemia risk coefficient and an RBE of 6 or 7 for alpha-particle induced leukemia (Hunacek and Kathren 1995, RAC 1999). Based on ICRP dosimetry models, an RBE of this magnitude would imply that the calculated leukemia risk from alpha emitters of greatest interest – *i.e.*, those depositing in/on the mineral phase of bone – would be comparable to the estimated bone sarcoma risk. However, studies of radium dial painters who had ingested ^{226}Ra and of patients injected with ^{224}Ra indicate that the risk of leukemia induction by such alpha emitters is small compared to the risk of bone sarcoma (Mays *et al.* 1985, NAS 1988). These findings imply an RBE of no more than about 1 for leukemia induction.

The alpha particle dose is quite different for the Thorotrast patients from that for the radium exposed cohorts. The ^{232}Th is incorporated into colloidal particles which are suspended in the marrow rather than being deposited in the bone mineral phase. Some of the marrow is effectively screened from alpha particles emitted from the bone surface. The Thorotrast particles may, therefore, more effectively irradiate target cells in the marrow, leading to a higher leukemia risk for a given average marrow dose.

In conclusion, for what are generally the most important cases of interest *(i.e.,* alpha-emitting radionuclides deposited in/on the mineral bone) the risk of leukemia appears to be small compared to the bone sarcoma risk. An effective RBE of about 1 seems to provide an upper bound on the leukemia risk. The multiplicative error associated with the uncertainty in these cases is assigned a uniform distribution U(0,1). We would emphasize that this reflects the uncertainty in what is basically an “effective RBE,” which factors in the nonuniform distribution of energy deposition in the bone marrow; in no way does it imply that the target cells in the marrow are less sensitive to high-LET radiation than to gamma rays.

Ordinarily, leukemia induction by alpha-emitters not deposited in/on bone constitutes a relatively small fraction of the total (whole-body) risk from these radionuclides. Nevertheless a different uncertainty distribution is appropriate. Taking into account both the Thorotrast data and the evidence from neutron irradiated animals, a central estimate for the RBE of 3 and a range (approximate 95% confidence interval) from 1 to 10 seems reasonable (RAC 1999); accordingly, an RBE uncertainty distribution LN(3,1.7) is judged to be reasonable for leukemia induction by these radionuclides.

Lung is another site for which there are both low-LET data (from the LSS) and high-LET data (from radon exposed underground miners) on humans. The latter pertain almost entirely to adult male exposures. For adult males, the two sets of data are reasonably consistent with an RBE of roughly 10, but childhood and female exposures among the bomb survivors appear to be associated with higher relative risks than those for adult males (Shimizu *et al.* 1990). This contrasts with the BEIR IV/EPA radon risk model, which posits no dependence of the relative risk coefficient on sex or age at exposure. In conclusion, one cannot at this time properly assess whether or not a single model can be used for calculating the risk of both low-LET and high-LET (radon) exposures. Until such a model gains acceptance, one cannot unequivocally assign a single RBE value to lung cancer induction based on the epidemiological data.

Experiments comparing beagles inhaling particulates of alpha or beta emitters suggest an RBE of 33 to 58 for the lung (Griffith *et al.* 1987). However, the effect per unit dose from the beta emitters decreased rapidly with dose in these experiments, reflective of a high DDREF for low-LET radiation. EPA risk estimates for humans, on the other hand, are based on a DDREF of 2. Consequently, the dog experiments–if they are relevant to humans–are more suggestive of an overestimation of low dose, low-LET risk than an underestimation of high-LET risk for the lung. We have, therefore, adopted the same uncertainty distribution for RBE in the case of the lung as for other solid tumors (*i.e.,* a lognormal distribution with a 90% CI from 5 to 40).

Two other sites for which there are human data on alpha-particle risk are bone and liver, but direct human information on low-LET risks for these sites is sparse. Consequently, for these sites, high-LET risk estimates are based directly on the human data, whereas the corresponding low-LET risk estimates are obtained by dividing the high-LET estimates by a nominal alpha-particle RBE of 20. In general, liver and bone risk do not constitute a major portion of the total risk from intake of beta/photon emitters. Thus, while the uncertainty in low-LET risk for these sites would be strongly influenced by the uncertainty in alpha-particle RBE, these uncertainties are not important from a practical standpoint, since they are not major contributors to the overall uncertainty in risk from any likely low-LET exposure. [Note: Citing animal data published by Lloyd *et al.* (1995), RAC (1999) assigned a 97.5% upper confidence bound of 375 to the alpha-particle RBE for bone. Even for ingestion of a bone-seeker like ^{90}Sr, inclusion of this extreme upper bound RBE would only slightly perturb the lower bound total cancer risk estimate.]

Finally, in assessing risks from short-range alpha particle radiation, attention must be paid to possible nonuniformity in both the doses and the radiation sensitivity within target tissues. This point has already been discussed above with respect to the induction of leukemia by bone-seeking radionuclides. With respect to the induction of bone cancer, too, it is necessary to evaluate the dose to the target (endosteal) cells residing on the bone surface, which may be quite different from the average dose to the bone (Puskin *et al.* 1992). Another important case is the nonuniform dose to cell

systems within the lung delivered by radionuclides deposited in the respiratory system, and the widely varying sensitivity of these cells to radiation. In such instances, great care is required in extrapolating from low-LET information, where the dose is fairly uniform within the tissue. Application of simple RBE factors derived from animal studies without proper consideration of the dosimetric issues can easily lead to fallacious conclusions about the magnitude of the risk and the range of uncertainty.

H. Uncertainty in Whole-Body Risk

In general, radionuclide exposures produce a nonuniform distribution of dose within the body. The uncertainty in risk associated with the exposure depends on the uncertainty in organ specific doses as well as the uncertainty in the risk per unit dose for each organ irradiated. It is outside the scope of this document to assess the uncertainty in risk estimates for specific radionuclides and exposure pathways. The main purpose here is to provide a framework for assessing the uncertainty in organ specific risk, for specified dose distributions. This general framework has been applied elsewhere to assess the uncertainty in risk from ingested radon-222 in drinking water (EPA 1993).

A commonly encountered exposure scenario is one in which there is an approximately uniform, whole-body dose of low-LET radiation. Examples would include: (1) external exposure to energetic x-rays or gamma rays and (2) ingestion of Cs-137 or tritiated water, where the radionuclides are distributed fairly uniformly throughout the body. As stated in Section II, the estimated risk from a uniform, whole-body, low dose rate exposure is 5.75×10^{-2} fatal cancers Gy^{-1}. In this section we assess the uncertainty in this risk estimate, based on the discussion of uncertainties in organ specific risk estimates presented above.

To quantify the overall uncertainty in the nominal estimate of risk, we treat the various component sources of uncertainties as independent multiplicative factors, each with its own probability distribution. For whole-body irradiation the estimate of risk rests mainly on results from the LSS. Accordingly, this uncertainty analysis will focus on the uncertainty in the data and model projections derived from the LSS. These components of uncertainty include: (1) sampling variation in the LSS; (2) the model used to project risk over time; (3) the transport of risk from the LSS to the U.S. population; (4) errors in A-bomb dosimetry; (5) the value of the DDREF; and (6) errors due to diagnostic misclassification.

1. Sampling variation

From Table 2, the relative standard error in the estimate of all cancers other than leukemia is about 15%. The relative standard error for leukemia is only slightly higher; moreover, the leukemia risk constitutes only about 10% of the risk from uniform, whole-

body irradiation. Thus, it should be adequate to estimate the uncertainty due to sampling variation based on the data for solid tumors. This source of uncertainty is well represented by a multiplicative factor, x_1, normally distributed with a mean of 1.0 and a standard deviation of 0.15.

2. Diagnostic misclassification

As outlined in Section B, the multiplicative error in the whole-body risk estimate due to diagnostic misclassification in the A-bomb survivor study (x_6) will be represented by a normal distribution N(1.2,0.06).

3. Temporal dependence

As discussed above, some of the organ specific risk projections are dependent on a lifetime extrapolation of very high relative risks seen among those exposed as children. To an extent these estimates are based on poor statistics; also, there are some theoretical reasons and empirical observations to suggest that the relative risks will decrease over time. Hence, as discussed in Section C, the population risks may be overestimated by about a factor of 2 or more. Conversely, for some organs, the risk estimates are dominated by data on adult exposures, possibly leading to an underestimate of the risks to the general population including children. Generally, however, these organs include only ones for which the risks are fairly low, together accounting for only 14% of the whole-body risk. Thus, if risks for these sites are underestimated by as much as a factor of 1.5 (see Section C), the whole-body risk would only be increased by 7%.

As a result, the error induced by temporal projection is likely to be in the "conservative" direction. This uncertainty is characterized here by a multiplicative factor (x_2) with a probability density given by a trapezoidal function Trpz(0.5,0.6,1.0,1.1). The probability density in this case increases linearly from zero to a maximum as x_2 increases from 0.5 to 0.6, remains constant over the interval from 0.6 to 1.0, and then decreases linearly to zero as x_2 approaches 1.1.

4. Transport of risk estimates

Our analysis of this uncertainty is predicated on the assumption that the multiplicative and NIH projections from the LSS provide upper and lower bounds on the transport uncertainty for each cancer site. As shown in Table 4, sites differ as to which projection is higher or lower. In general, there are little or no data to support one projection model over the other, and the multiplicative model may be better for projecting some organ risks, whereas the NIH model may be more suitable for others. For some organs a correct projection may fall between the two model projections.

TABLE 4

Multiplicative, NIH and GMC projections of specific organ risks (deaths per 10^4 person-Gy)

Cancer Site	Multiplicative	NIH	GMC
Esophagus	9.16	15.7	11.7
Stomach	12.7	135	40.7
Colon	185	62.8	104
Lung	194	52.7	98.8
Ovary	26.2	8.89	14.9
Bladder	30.6	19.3	23.8
Leukemia	54.3	50.9	55.7
Remainder	185	146	149

An extreme upper (lower) bound on the "transport uncertainty" can be obtained by choosing for each site the multiplicative or NIH projection, whichever is higher (lower), and then summing over all sites. Less extreme estimates of the uncertainty bounds can be obtained through a Monte Carlo procedure in which the projection for each site is allowed to vary randomly within the limits defined by the multiplicative and NIH projections for that site, and then summing over sites. The resulting projection will depend on assumptions regarding the mathematical form of the uncertainty distribution for the individual sites and possible correlations between sites (*e.g.*, if the multiplicative projection were known to hold for one site, this may increase the probability that it would hold for other sites, as well).

For those sites which the GMC estimate has been adopted (*i.e.*, esophagus, stomach, colon, lung, ovary, bladder, leukemia, and residual), we assume that the distribution of uncertainty is loguniform between the NIH and multiplicative projections, and that the transport with respect to different sites is independent. A Monte Carlo calculation then shows that the uncertainty in the whole-body risk estimate associated with the transport of risk estimates is distributed approximately symmetrically about a mean estimate, which is about 10% higher than the nominal estimate, and with a standard deviation of about 12%. Accordingly, a normal distribution is assigned to this

multiplicative uncertainty factor (x_3), with a mean of 1.1 and a standard deviation of 0.12.

5. Errors in dosimetry

Based on information presented in Section E, the multiplicative uncertainty (x_4) associated with errors in dosimetry is assumed to follow a normal distribution [N(0.84,0.11)] with mean 0.84 and standard deviation 0.11.

6. Error in the choice of DDREF

The value of the DDREF (x_5) is drawn from the distribution defined by Equations 2a and 2b in Section F. The probability density is uniform for $x \in [1, 2]$, falling off exponentially for x>2 (see Figure 1a).

7. Calculation of uncertainty

Table 5 summarizes the sources of error considered here in estimating the uniform whole-body risk and the assumed probability distribution for each. Treating each of these sources of error as independent and multiplicative, but noting that the DDREF divides rather than multiplies the risk and that a DDREF of 2 is already incorporated into the risk estimate, a Monte Carlo calculation was carried out (see Table 5 caption). The results showed that the uncertainty was distributed approximately lognormally, with a median risk estimate of 4.9×10^{-2} fatal cancers/Gy and a geometric standard deviation (GSD) of about 1.66; the mean of the distribution is 5.4×10^{-2} Gy^{-1}. The estimated 90% subjective confidence interval is 2.0×10^{-2} -1.1×10^{-1} Gy^{-1}.

Thus, based on the results of the uncertainty analysis, the nominal estimate is biased high, but only slightly. The actual risk is expected to be no more than about a factor of 2 times higher or 3 times lower than the nominal estimate of 5.75×10^{-2} Gy^{-1}. The estimated bias mainly results from the assumed form of the temporal dependence in our risk model: *i.e.,* a constant relative risk. Overall, the most important uncertainties seem to be in the temporal dependence of the risk (especially for childhood exposures) and in the DDREF.

TABLE 5

Distributions used to estimate the uncertainty in the risk of low level, low-LET, whole-body irradiation

Source of Uncertainty	Distribution
Sampling variation (f_1)	N(1.0,0.15)
Diagnostic misclassification (f_2)	N(1.2,0.06)
Temporal dependence (f_3)	Trpz(0.5,0.6,1.0,1.1)
Transport across populations (f_4)	N(1.1,0.12)
Errors in dosimetry (f_5)	N(0.84,0.095)
DDREF (f_6)	U(1,2): 50% EXP(>2): 50%

Notes

(1) The combined multiplicative uncertainty distribution was generated by repeatedly sampling each of the distributions in the table and calculating the value of $(x_1\ x_2\ x_3\ x_4\ x_5)(2/x_6)R$, where the x_i denote random values of the independent variates defined by the distributions f_i, and where R is the nominal low dose, whole-body risk estimate, 5.75×10^{-2} fatal cancers Gy^{-1}.

(2) For the normal distribution, the parameters in parentheses refer to the mean and standard deviation, respectively. The trapezoidal distribution, Trpz(a,b,c,d) rises linearly from zero to a maximum as the random variable x_i increases from a to b; remains constant for $b<x_i<c$; and then decreases linearly to zero as x_i increases from c to d.

(3) The probability density function f_6 is defined by Equations 2a and 2b, or by Figure 1a: The distribution is uniform between 1 and 2, falling off exponentially to zero for $x_5 > 2$; the median of the distribution is assumed to be 2.

I. Uncertainty in Incidence Estimates

In most cases, site-specific incidence estimates reflect mortality risk estimates divided by the cancer lethality estimate for the site in question (see Section IV.F of EPA94). For those sites contributing most heavily to the whole-body risk (*e.g.*, lung and colon), the possible error in lethality is small compared to

the uncertainty in the radiogenic cancer risk estimate for that site. One exception is radiogenic leukemia, where the use of a lethality fraction of 99% (EPA94, Table 5) understates the cure rate achievable with modern medicine, especially for children. As noted in Section IV.F of EPA94, this would likely produce an overestimate of the mortality rather than an underestimate of the incidence.

Another issue relates to the estimate of skin cancer incidence. Nonfatal skin cancers, most of which are of little clinical significance, were not included in the estimate of incidence. If–as often occurs for external exposure to a beta emitter–the dose is predominantly to the skin, inclusion of all these nonfatal cases could increase the incidence estimate by up to a factor of 500 (see: EPA94, Section IV.D). For uniform whole-body irradiation, the total cancer morbidity estimate would be increased from 850×10^{-4}/Gy to 1350×10^{-4}/Gy. A small fraction of nonfatal radiogenic skin cancers are serious in that they require substantial medical intervention and may result in significant residual impairment or disfigurement. Although there appear to be no published estimates of this fraction, it is not expected that inclusion of these serious nonfatal cases would appreciably increase the incidence for uniform, whole-body irradiation. However, in cases where the dose to the skin is high compared to other organs, inclusion of the serious nonfatal cases might increase the incidence by as much as an order of magnitude.

A comparison between Japanese A-bomb survivor incidence and mortality data has recently been published (Ron *et al.* 1994). The authors conclude that:

> For all solid tumors the estimated excess relative risk at 1 Sv...for incidence...is 40% larger than the excess relative risk (ERR) based on mortality data... For some cancer sites, the difference...is greater. These differences reflect the greater diagnostic accuracy of the incidence data and the lack of full representation of radiosensitive but relatively nonfatal cancers, such as breast and thyroid, in the mortality data.

To date, the Japanese incidence data have not been used to develop comprehensive risk projections for other populations. It seems likely, however, that the Japanese incidence data will increasingly serve as a basis for radiogenic cancer risk estimates in the future.

J. Numerical Estimates of Uncertainty in Specific Organ Risks

Quantification of the uncertainties in all the site-specific cancer risk estimates is beyond the scope of this document. However, for illustrative purposes, we shall attempt to quantify the uncertainties in the low-LET cancer

mortality risk estimates for two cancer sites: lung and bone marrow. These two sites are of particular interest because they are often "critical organs": *i.e.*, for certain radionuclides and pathways, the highest projected organ-specific risk is associated with one of these sites.

1. Uncertainty in lung cancer risk estimate

Sampling variation. As shown in Section A, the nominal estimate of the ERR/Gy is 0.63 with a 90% confidence interval of 0.35 to 0.97. A simple approximation to the distribution is given by a normal distribution with a mean of 0.66 and standard deviation 0.19. Normalizing the nominal estimate to unity, the uncertainty is given by a multiplicative factor N(1.05,0.29).

Diagnostic misclassification. A comparison of autopsy and death certificate diagnoses indicates that diagnostic misclassification of lung cancer among the LSS cohort is high, especially for persons over age 75 (Ron *et al.* 1990). Moreover, the ERR/Sv for lung cancer incidence, as determined from Hiroshima and Nagasaki tumor registry data between 1958-1987, is about 42% higher than the corresponding ERR/Sv for mortality, as determined from death certificates collected over the same time period (Ron *et al.* 1994). Since lung cancer is rapidly fatal in a high percentage of cases, this would seem to indicate that diagnostic errors are substantially perturbing the ERR estimates. The incidence determinations are believed to be more accurate than the death certificate information. It is therefore likely that our risk estimates, which are based on mortality data, are biased low due to diagnostic misclassification. As a subjective estimate of the error due to diagnostic misclassification of lung cancer, we assign a multiplicative uncertainty factor N(1.3,0.15) to this source of error.

Temporal dependence. As discussed in Section C, an uncertainty distribution U(0.5,1.0) is assigned to this source.

Transport of risk estimate from LSS. As shown in Table 4, the multiplicative and NIH model projections for radiogenic lung cancer mortality are, respectively, 194/98.8 = 1.96 and 52.7/98.8 = 0.53 times that of the nominal estimate. Accordingly, a multiplicative uncertainty factor LU(0.5,2.0) will be assigned to the transport of the risk estimate from the LSS to the U.S. population [see Section D]. This transport is thus a much larger source of uncertainty for the lung cancer risk than for the whole-body risk [see Section H.4].

Errors in dosimetry. The analysis of uncertainty in whole-body risk associated with errors in dosimetry incorporated four sources of uncertainty in DS86 (see Table 3). In order to derive an uncertainty distribution for lung dosimetry, one of the four underlying distributions, that associated with neutron

dose, needs to be modified. For whole-body irradiation, the distribution was triangular, with a peak at 1.10 and a range of 1.0 to 1.3. This distribution, however, was based on dose to the colon; transmission of radiation to the lung is considerably higher than to the colon. According to Table 4B-1 of the BEIR V Report (NAS 1990), the transmission factors for the colon are 0.74 and 0.19, for gamma rays and neutrons, respectively; the corresponding values for the lung are 0.80 and 0.33.

To see the effect of transmission factors on the dosimetric uncertainty, consider the colon dose to an arbitrary survivor. DS86 neutron doses are relatively unimportant (NAS 1990) so we can approximate the dose as:

$$D_C = D_{C\gamma}$$

The corrected dose (with neutrons added) can be written:

$$D_C' = D_{Cn} + D_{C\gamma}'$$

where D_{Cn} is the weighted neutron dose to the colon and $D_{C\gamma}'$ is the γ-ray dose, corrected for the increase in neutron flux. Neglecting the small contribution to the γ-ray dose from n,γ reactions, $D_{c\gamma}' = D_{c\gamma}$, and these equations imply:

$$D_C'/D_C = 1 + D_{Cn}/D_{C\gamma} = 1 + X_C$$

Similarly, for the lung, we would have:

$$D_L'/D_L = 1 + D_{Ln}/D_{L\gamma} = 1 + X_L$$

Using the transmission factors above, the fractional increment to the lung dose can then be compared to that for the colon:

$$X_L/X_C = (0.33/0.19)(0.74/0.80) = 1.61$$

Thus, the neutron correction to the lung dose is about 61% larger than for the colon. Scaling the uncertainty distribution based on colon dose appropriately, the uncertainty distribution for the lung due to underestimation of neutron dose is triangular with a range from 1 to 1.483 and peaked at 1.161.

With this modification to the distribution $f_5(D)$ in Table 5, the uncertainty factor for lung cancer risk due to dosimetric uncertainties is found, by Monte Carlo simulation, to be approximately normal, with a mean of 0.72 and a standard deviation of 0.093.

Extrapolation to low doses and dose rates. Assigning an uncertainty distribution to the DDREF for lung cancer is problematic. On the one hand, the dose response in the A-bomb survivor cohort shows no sign of nonlinearity (Thompson *et al.* 1994). On the other hand, a study of lung cancer mortality in Canadian tuberculosis patients receiving highly fractionated doses of radiation (through fluoroscopy examinations) revealed no excess risk of lung cancer (Howe 1995).

The upper 95% confidence limit on the ERR/Sv in the fluoroscopy patients was only about one-ninth the central estimate based on the A-bomb survivors and only about one-fourth the corresponding 95% lower confidence estimate. Although Howe concludes that the discrepancy is most likely attributable to the dose fractionation, other factors may be important. In particular, Howe's comparison presupposes that relative risk transports from one population to another (multiplicative projection model). As discussed above, the NIH projection model would reduce the projected risk for a North American population by roughly a factor of 4. Taking this into account, the data are consistent with a DDREF of about 2. As noted in Section F, moreover, other differences in the populations might further contribute to the discrepancy; *e.g.*, differences in the age distribution of the exposed populations and possible confounding by the lung disease present in the fluoroscopy subjects.

Thus, while the fluoroscopy data suggest a large reduction in lung cancer risk at low dose rates, the case is not compelling. So long as the large uncertainty in "risk transport" is factored into the analysis, it seems reasonable to adopt for lung cancer the default DDREF uncertainty distribution, defined by Equations 2a and 2b in Section F.

Calculation of the uncertainty in low dose lung cancer risk. Table 6 summarizes the distributions assigned to each multiplicative uncertainty factor for lung cancer risk. Following the same Monte Carlo procedure used for whole-body irradiation in Section H.7, we arrive at an overall 90% subjective confidence interval of 2.0×10^{-3} Gy^{-1} to 2.0×10^{-2} Gy^{-1}. The median and mean of the uncertainty distribution are 6.7×10^{-3} Gy^{-1} and 8.3×10^{-3} Gy^{-1}, respectively. Thus, it is estimated that the actual lung cancer risk could be about a factor of 2 higher or a factor of 5 lower than the nominal estimate of 9.9×10^{-3} fatal cancers/Gy, a significantly wider range than for the whole-body risk (cf. Section H.7). Primarily, the wider range reflects the greater transport uncertainty in the case of lung cancer risk.

TABLE 6

Distributions used to estimate uncertainty in risk of lung cancer mortality from low dose irradiation of the lung

Source of uncertainty	Distribution
Sampling variation	N(1.05,0.29)
Diagnostic misclassification	N(1.3,0.15)
Temporal dependence	U(0.5,1.0)
Transport across populations	LU(0.5,2)
Errors in dosimetry	N(0.72,0.093)
DDREF	U(1,2): 50% EXP(>2): 50%

2. Uncertainty in leukemia risk estimate

Sampling variation. Compared to other sites, the sampling errors for leukemia risk are relatively small. Based on the data in Table 2, we assign an uncertainty factor N(1.05,0.18) to sampling errors.

Diagnostic misclassification. Diagnosis of leukemia in the A-bomb survivors has been found to be relatively accurate (Ron *et al.* 1994). Diagnostic misclassification has therefore been neglected in this uncertainty analysis.

Temporal dependence. The temporal response observed in the LSS for leukemia is complex, being dependent on city, sex, age at exposure, and type of leukemia (Preston *et al.* 1994). From an examination of the trends in the data, it would appear that relatively few excess cases are expected beyond the current period of epidemiological follow-up (Pierce *et al.* 1996). In addition, since leukemia data on the A-bomb survivors were not collected before 1950, a temporal projection is also required for the period 0-5 years after exposure. Again, based on a mathematical extrapolation from the observed cases, it is projected that only about 10-15% of the leukemias occurred in the A-bomb survivors during the initial 5-yr period (Preston *et al.* 1994). This would suggest that the backward temporal projection is not a major source of uncertainty. However, other studies give conflicting results. Among irradiated cervical cancer patients, all of the excess

leukemias were observed within the first five years post exposure (Boice *et al.* 1987) . In the ankylosing spondylitis cohort, more than half of all excess leukemias were observed in the first five years of follow-up (Darby *et al.* 1987, NAS 1990). These results suggest that the backward extrapolation from the A-bomb survivor data may significantly understate the risk during the first five years post exposure (NAS 1990).

BEIR V presents four alternative temporal projection models for leukemia (NAS 1990). The report's preferred model projects roughly twice the risk as the other three BEIR V models or the EPA leukemia model. Computer simulations show that this difference primarily reflects differences in projected cases within the (5-40 y) period of epidemiologic follow-up, rather than before 5 y or after 40 y. Thus, at least in the case of leukemia, there are appreciable temporal model uncertainties unrelated to the projection of risk outside the period of follow-up.

In conclusion, the temporal model may significantly understate the risk during the first five years post exposure, before data collection on the A-bomb survivors began. There is additional uncertainty in the risk projection over subsequent years due to uncertainties in the mathematical form of the age and temporal response function. To account for these uncertainties, we have subjectively assigned to the uncertainty factor for temporal projection a triangular-shaped probability distribution, peaked at 1, and extending over the range from 0.8 to 2.

Transport uncertainty. Removing chronic lymphatic leukemias from consideration since they are not regarded as radiogenic (NAS 1990), the overall leukemia incidence rates for Japan and the U.S. are similar. As a consequence, the risk estimates for the U.S. under the multiplicative and NIH projections differ only by slightly (see Table 4). This very close agreement may be partly fortuitous, resulting from a cancellation of differences between different types of leukemia whose risks are being summed. A subjective uncertainty distribution LN(1.0,1.15) has been assigned to the transport of risk from the LSS to the U.S. population.

Dosimetric errors. Like the lung, radiation transmission to the bone marrow is considerably higher than to the colon, the dose to which was used in calculating the dosimetric uncertainty for the whole body. The neutron transmission factor to the bone marrow is 0.37, nearly twice that for the colon, and 0.81 for γ-rays (Shimizu *et al.* 1989, NAS 1990). Following the procedure used for deriving the dosimetric uncertainty distribution in the case of the lung, the uncertainty factor associated with neutron dose is taken to be triangular with a range from 1.0 to 1.534 and peaked at 1.178. With this replacement, the combined uncertainty factor associated with bone marrow dosimetry is still approximately normal, but with a mean of 0.70 and a standard deviation of 0.096.

Extrapolation to low doses and dose rates. Pierce and Vaeth (Pierce and Vaeth 1991) have examined data on cancer mortality among the A-bomb survivors with the aim of determining the degree of curvature in a linear-quadratic dose-response model that is consistent with the data. From this analysis, they estimated the degree to which a linear extrapolation of the risk could overestimate the risk at low doses. The magnitude of the error is expressed in terms of a "low dose extrapolation factor" (LDEF), which is equivalent to the dose and dose-rate effectiveness factor (DDREF). Adjusting for random errors in dosimetry of ±35%, the maximum likelihood estimate for the LDEF was about 2.0 with respective 80, 90, and 95% one-sided confidence limits of about 3, 4.2, and 6.

Supplementary to data on the A-bomb survivors are reports of excess leukemia in populations exposed chronically to low-LET radiation. A best estimate of the leukemia risk in a combined cohort of nuclear workers from the U.S., UK, and Canada is about one-half that predicted from the linear model derived from the LSS data (Cardis *et al.* 1995). Although the uncertainty bounds are wide, these results are suggestive of a DDREF of about 2. Preliminary data on leukemia incidence among populations exposed occupationally or environmentally to radiation from the Chelyabinsk nuclear weapon facilities in the former Soviet Union indicate about a 3-fold reduction in risk at low dose rates (UNSCEAR 1993).

The preponderance of current data indicate that the DDREF for leukemia is about 2 or 3, but values as high as about 6 or as low as about 1 are not excluded. For the uncertainty analysis here, a lognormal distribution is assigned to the DDREF, with a GM of 2.5 and a GSD of 1.5.

Calculation of uncertainty in leukemia risk. Table 7 lists the sources of uncertainty in the leukemia risk at low doses and dose rates along with the probability distribution assigned to each source. Again utilizing the Monte Carlo procedure used for whole-body and lung cancer risks, an overall uncertainty distribution for the general population leukemia mortality risk was calculated. The 90% subjective interval of the distribution is 1.7×10^{-3} - 9.4×10^{-3} Gy^{-1}; the median and mean are 4.0×10^{-3} Gy^{-1} and 4.5×10^{-3} Gy^{-1}, respectively. Thus, similar to the case of uniform whole-body risk, the 90% subjective confidence interval for leukemia risk includes values as much as 3.3 times lower or 1.7 times higher than the nominal estimate (5.6×10^{-3} Gy^{-1}). The largest contributor to the uncertainty in leukemia risk is the uncertainty in low dose extrapolation (DDREF).

TABLE 7

Distributions used to estimate the uncertainty in leukemia risk from low dose irradiation of the bone marrow

Source of uncertainty	Distribution
Sampling variation	N(1.05,0.18)
Temporal dependence	T(0.8,1.0,2.0)
Transport uncertainty	LN(1.0,1.15)
Dosimetric errors	N(0.70,0.096)
DDREF	LN(2.5,1.5)

K. Discussion

The aim of this report is to provide quantitative estimates of uncertainty in EPA's radiogenic cancer risk estimates. Thus, we are concerned here with the uncertainties in only one portion of a radionuclide risk assessment: the dose-response model. For each of the cases analyzed in detail here (*i.e.,* low-LET risks to the whole body, to the lung, and to the bone marrow) the estimated 90% subjective confidence interval was relatively narrow – a factor of 5 to10 from the low to the high end of the interval. In general, however, to assess the overall uncertainty in risk, one must also consider uncertainties in exposure and dose. For a specific risk assessment, these latter uncertainties will often predominate.

The approach here was to treat the overall uncertainty in population risk as a product of independent "uncertainty factors," each of which defined the possible deviation of the nominal risk estimate from the "true" population average due to one specific source of uncertainty. This approach greatly simplifies the analysis and generally helps to clarify the relative importance of the various sources of uncertainty, but there may be some resulting inaccuracies. Of particular concern in this regard is the separation of the uncertainties due to sampling errors and those due to age and temporal modeling. Both these types of uncertainty are magnified for childhood exposures, which contribute a disproportionate part of the population risk. As a consequence, treating these two sources of uncertainty as independent may lead us to underestimate the uncertainty in the population risk. On the other hand, the uncertainty factors pertaining to different sources may sometimes be inversely correlated; in those cases, treating them as independent may produce overall uncertainty ranges that are too wide.

The greatest source of controversy in radiogenic cancer risk estimation remains the extrapolation to low acute doses and low dose rates. Current scientific data do not rule out the possibility that the risk per unit dose is effectively zero at environmental exposure levels, and proponents of an effective threshold or a protective effect of low dose radiation continue to argue their case vigorously (Luckey 1990, Jaworowski 1995, Goldman 1996). Our judgment–based on an examination and synthesis of information from molecular, cellular, animal, and human studies–is that there is at this time very little support for such an effective threshold or a protective effect, and they were excluded from consideration in arriving at our uncertainty bounds on risk.

Another approach to the problem of estimating the uncertainty relating to low dose rate extrapolation would be to elicit the judgment of experts as to the probability of different DDREF values and then to perform some kind of averaging of these results (NRC 1997). While potentially useful in bringing out a wider range of opinions and assumptions, this method is highly resource intensive, and it is unclear whether it would provide a "better" estimate of uncertainty than the method used here or in NCRP Report No.126, where a few analysts developed a probability distribution based on a broad review of the literature and modified it in light of comments from colleagues. Moreover, while the conclusions drawn here reflect subjective views of the authors, they are informed by those of various expert panels (NCRP 1997; UNSCEAR 1993, 1994; NRPB 1993, NRC 1997).

In addition, we would note that the risk estimates and uncertainty estimates presented here are predicated on a life table population and the published U.S. 1990 Vital Statistics. Any exposed population will differ from this idealized population. First, the age distribution will be different; *e.g.,* the actual U.S. population has a higher proportion of individuals in the younger age groups. Second, the baseline cancer incidence and mortality rates, as well as life expectancies, undergo continuous evolution, due to changes in lifestyle, medical care, etc. As a consequence, each birth cohort will experience a different risk, even if all cohorts are presumed to be chronically exposed at the same constant rate over their lifetime. Obviously, the use of current baseline rates becomes increasingly problematic as we project farther into the future. Third, baseline cancer rates for the U.S. population, like the LSS population, must be regarded as uncertain due to diagnostic misclassification. Such misclassification will clearly lead to errors in projecting radiogenic cancers in an exposed U.S. population based on a relative risk model.

Finally, we would emphasize that the risk and uncertainty estimates contained here reflect population averages. A more specific assessment could be carried out for each gender or age group, but information on other factors strongly affecting risk (*e.g.,* genetic susceptibility) may be lacking. Thus, the uncertainty in risk for an individual may be considerably larger than for a population.

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