Draft Report of the NCI-CDC Working Group to Revise

the 1985 NIH Radioepidemiological Tables

May 31, 2000

Members of the working group:

Charles Land (chairman) and Ethel Gilbert, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Jim Smith, Radiation Studies Branch, National Center for Environmental Health, Centers for Disease Control and Prevention

Consultants:

F. Owen Hoffman, Iulian Apostoaei, and Brian Thomas, SENES Oak Ridge, Inc.

Advisors:

Pat Buffler, U. of California (Berkeley);
Lars-Erik Holm, Swedish Radiation Protection Institute;
Jerome S. Puskin, EPA Office of Radiation and Indoor Air;
Dan Schafer, Dept of Statistics, Oregon State University;
Lincoln Grahlfs, Atomic Veterans Association;
Seth Tuler, Social and Environmental Research Institute

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I. Executive Summary

The legislative mandate for the 1985 Report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables provided for analyses of existing data linking cancer risk to ionizing radiation exposure, to facilitate the adjudication of compensation claims for cancers diagnosed following exposure to ionizing radiation. The 1985 working group did this by estimating "probability of causation" (PC) values, defined as

$$PC = \frac{\text{Risk due to radiation exposure}}{\text{Baseline risk + risk due to radiation exposure}}$$

for hypothetical instances of cancer following specific histories of radiation exposure. The report has been used mostly by the Department of Veterans Affairs (VA) as a guide to adjudicating compensation claims for cancers diagnosed in persons who were exposed during military service. The amount of new information about radiation-related cancer risk has increased markedly during the 15 years since publication of the report, and there have been revisions in the system of dose reconstruction used for the major source of epidemiological data for estimating risk, the cohort of atomic bomb survivors studied by the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. The VA requested the Secretary of the Department of Health and Human Services (DHHS) to update the Report, as provided for in the original legislative mandate, and joined with the DHHS to support the present effort by a working group of the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC).

Noting that the National Academy of Science/National Research Council (NAS/NRC) Committee on Biological Effects of Ionizing Radiation (BEIR VII, phase 2) is expected to complete within 2 or 3 years a comprehensive survey of the scientific data linking radiation exposure to health effects in human beings, the NCI and CDC have undertaken to provide an interim update of the 1985 report based on statistical analyses by the working group of readily available data on cancer risk following radiation exposure, notably the 1958-87 LSS Tumor Registry data on survivors of the atomic bombings of Hiroshima and Nagasaki made available on computer disk by RERF. It is expected that a further update to the present report will be made following the BEIR VII review. The working group has replaced the tabular format of the 1985 report by an interactive computer program (IREP, for "interactive radio-epidemiological program") that eliminates nearly all of the computational labor of estimating PC values and their uncertainties, and permits a more detailed and comprehensive expression of the various components of the calculation and their uncertainties.

It has been argued, notably by the NAS/NRC oversight committee that provided critical advice to

the 1985 NIH working group (NAS, 1984), that the PC values calculated according to the formula given at the beginning of this summary pertain to populations rather than individuals, and that they "are not probabilities in the usual sense and are truly properties of the group to which a person belongs, but in practice are assigned to the person for purposes of compensation." The oversight committee recommended a change in terminology, replacing "probability of causation," by "assigned share" (AS) to emphasize the difference. The NIH working group did not disagree, but continued to use "PC" because the term was already in common use. The present working group feels that the oversight committee's point is worth repeating, and has chosen to use "AS" throughout its report. More generally, the working group emphasizes that the AS values obtained using the report and its computer program represent a summary of scientific findings about cancer risk following radiation exposure, that may be relevant to adjudication of individual claims, but that the report makes no claims regarding the influence of individual factors that have not been extensively studied.

It has also been argued by Greenland (1999) and others that AS is a logically flawed concept, subject to substantial bias and therefore unsuitable as a guide to adjudication of compensation claims in cases of possibly radiation-related cancer. The argument is based largely on the possibility that radiation exposure may accelerate the time of appearance of cancers that, in the absence of exposure, would have occurred later. The conclusion of the present working group, as discussed in the text of this report, is that the argument is unpersuasive in the light of current information about radiation-related risk. Scientific consensus about cancer risk following radiation exposure is constantly evolving as new information is uncovered. This is a time of rapid developments in our understanding of the carcinogenic process, and future developments may force a fundamental changes in our view of radiation carcinogenesis. For the present, however, the working group feels that current models are relevant both to radiation protection and the adjudication of claims for possibly radiation-related instances of cancer.

The focus of this report is on quantitative expression of uncertainty in AS, reflecting statistical uncertainty about risk estimates and more subjective uncertainty about model assumptions necessary to apply such estimates to the adjudication of compensation claims for cancer diagnosed following radiation exposure in the United States. In the U.S., unlike the United Kingdom where a voluntary "Compensation Scheme for Radiation-linked Diseases" allows for proportional compensation for AS values as low as 20% (Wakeford, 1999), adjudication of claims revolves around the likelihood that AS may exceed 50%. When there is a policy bias ("benefit of the doubt") in favor of the claimant, focus is on upper credibility limits for AS rather than on a central estimate. For example, present VA policy is to award claims for which the upper 99% credibility limit for AS is 50% or higher.

Uncertainty, including the statistical uncertainty inherent in estimates obtained by fitting observational data to theoretical models and subjective uncertainty inherent in model assumptions, is the primary focus of this report. One of the many advantages of replacing tables by an interactive computer program is that much more detail can be made easily available to the user, including a complete representation of the uncertainty pertaining to a particular AS estimate.

The 1985 NIH report dealt with 13 different cancer sites for which there was strong statistical evidence of a radiation dose response in human populations. However, lack of a statistically significant dose response for a particular cancer type does not preclude a compensation award based on an upper credibility limit for AS. For example, the upper 99% credibility limit for AS can be greater than 50% even if the radiation dose response is not statistically significant (or even if, in extreme cases, the point estimate is less than zero). The present report is based on the working assumption that any type of cancer can, in principle, be induced by radiation, and that the most important question concerns the magnitude of the risk associated with particular exposures. In all, 33 different cancers and groups of cancers are treated, including several cancer types not significantly associated with radiation dose. The report does not include malignant melanoma and chronic lymphocytic leukemia, for which adequate data were lacking, or non-melanoma skin cancer, for which U.S. population baseline rates are unavailable. Lung cancer associated with radon exposure was not included because the most authoritative risk estimates, published by the NAS/NRC BEIR VI Committee (NAS, 1999) were judged not to be easily adaptable for AS purposes and to require more computational and staff resources than those available to the present working group.

Treatment of uncertainty in the updated report is guided by that in the original report and by more recent analyses, notably two publications of the National Council on Radiation Protection and Measurements (NCRP): Commentary 14 (NCRP, 1996), "A guide for uncertainty analysis and dose and risk assessments related to environmental contamination," and Report 126 (NCRP, 1997), "Uncertainties in fatal cancer risk estimates used in radiation protection." Essentially, the method involves calculation of an uncertain excess relative risk (ERR = excess risk/baseline risk) for the cancer of interest, as a function of radiation dose for each exposure. Other factors, represented by a series of randomly distributed factors which are assumed to be statistically independent, depend on informed but nevertheless subjective judgments from published reports of expert committees or by the authors of this report. They are designed to contribute bias correction and expression of additional uncertainty to a Monte Carlo simulation which provides a corrected ERR estimate, expressed as the product of all factors, and its uncertainty distribution combining all sources of uncertainty. If more than one exposure is involved, separate ERR

values and uncertainty distributions are calculated for each exposure, and combined. The overall ERR is then transformed to obtain the AS:

$$AS = ERR/(1+ERR).$$

Credibility limits for the AS are obtained as percentiles of its uncertainty distribution.

The various factors contributing to the overall estimate, and its uncertainty, are as follows:

ERR per unit of dose (or dose plus dose-squared) and its statistical uncertainty distribution are taken from the tabulated likelihood curve obtained as the final output of statistical model fitting performed by the working group. If the dose response varies by age at exposure, age at diagnosis, or time following exposure, the ERR per unit dose may be interpolated among different likelihood curves corresponding to different values of these variables. ERR per unit dose, as estimated, may be influenced by random and systematic errors in A-bomb survivor dosimetry, requiring several uncertain bias correction factors. Radiation dose for the claimant is entered by the user, either as a known value or as an uncertain value with a user-specified uncertainty distribution. Doses received at low doses and dose rates are adjusted by a factor (with uncertainty) known as the dose and dose rate effectiveness factor (DDREF), which may reduce the ERR per unit dose of gamma ray or other sparsely ionizing radiation. The DDREF does not apply to neutrons, alpha particles, or other kinds of densely ionizing radiation which are thought to have greater biological effects than sparsely ionizing radiation and are weighted accordingly. A separate factor is used to express the uncertainty of this weighting, which may depend upon type of radiation and the type of cancer.

Site-specific baseline risks for many cancers differ substantially between Japanese and US populations, and there is considerable uncertainty about how this affects risks resulting from radiation exposure. A complex and highly uncertain factor is required for transfer of risk estimates from A-bomb survivors to a US population. Tobacco smoking is known to modify the carcinogenic effects of radiation to the lung, requiring an uncertain adjustment factor. Finally, an additional factor is included for miscellaneous sources of uncertainty for AS in populations (not in individuals).

The present report is considered to be an interim update of the 1985 NIH report. Like that report, its AS estimates are based primarily on A-bomb survivor data. The present working group has had the advantage of access to comprehensive cancer incidence data from a greatly improved RERF Tumor Registry, which are not only more recent but are based on more timely and more accurate diagnoses than those available from death certificates. Incidence data are also more relevant to compensation claims for cancers of delayed or low fatality. Direct access to RERF

data allowed the working group to conduct its own analyses directed at the needs of this report, including modeling of dose-response modifiers such as age at exposure, and inclusion of cancer types not significantly associated with radiation exposure.

Unlike the 1985 report, the current report is based on linear dose-response models for all solid cancers, with an uncertain DDREF factor to allow for the possibility that risk per unit dose decreases with decreasing dose and dose rate. This approach is not necessarily better than the linear-quadratic model approach used previously, but it is accord with recent recommendations by expert committees. Also, the present report treats relative biological effectiveness of densely cf. sparsely ionizing radiation as an uncertain quantity. The present report's treatment of the problem of transfer of estimates between populations with different baseline rates is an important change, and accounts for a large part of the total uncertainty for several sites.

As previously mentioned, this is an interim report which is expected to be modified as new information on radiation-related risk becomes available. It is hoped that the *form* of the report may prove to be of more lasting value. In particular, the IREP program is constructed to allow - new risk estimates and statistical uncertainty distributions to replace old ones, for new cancer sites to be added, and for the treatment of other sources of uncertainty to be modified. The program will be made available for use from an NCI web site, and will be maintained and revised as necessary and appropriate.

II. Background of 1985 report

A. Congressional mandate and its execution

On January 4, 1983 the President of the United States signed Public Law 97-414 (known as the "Orphan Drug Act"), an act to amend the Federal Food, Drug and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes. This legislation includes a provision (Section 7 (b) of the bill) directing the Secretary of Health and Human Services (DHHS) to "devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses." The mandate included a provision for periodic updating of the tables.

It may be noted that the section of P.L. 97-414 pertaining to the development of radioepidemiological tables originally was introduced by Senator Orrin Hatch (Utah) as a part of Senate bill S 1483: "Radiation Exposure Compensation Act" to provide for damages due to radiation exposure from nuclear weapons tests in Nevada. Since neither this bill nor the companion House bill (H.R. 6052) was reported out of the respective committees, the section relating to radioepidemiological tables was attached as an amendment to the "Orphan Drug Act" which was passed by both houses and signed into law on January 4, 1983. The complete text of section 7 (b) of the bill and an excerpt from President Reagan's statement, on the occasion of his signing the Orphan Drug Act, are given in Appendix A of the present report.

Lead responsibility for the implementation of the enacted charge was assigned to the National Institutes of Health (NIH) by the Assistant Secretary of Health, DHHS, who also requested that a National Research Council (NRC) committee be formed to review the recommendations of the NIH. Subsequently (August 4, 1983), the Secretary of Health and Human Services approved the Charter for an "Ad Hoc Working Group to Develop Radioepidemiological Tables" to carry out this mandate. The text of the Charter is included as Appendix B.

An Ad Hoc Working Group, chaired by Dr. J. E. Rall, Deputy Director for Intramural Research, NIH, was established to carry out the work. The NIH contracted with the National Academy of Sciences (NAS) for the formation of an Oversight Committee in the NRC's Commission on Life Sciences, with the cooperation of the Institute of Medicine. The oversight committee, chaired by Prof. Frederick Mosteller of Harvard University, reviewed the data sources, assumptions, and methods of the NIH working group, and discussed wider issues regarding the tables in the context of their intended and possible uses. The report of the oversight committee was published in 1984 and the report of the working group was published on January 4, 1985.

B. "Assigned share"

The National Academy of Sciences committee charged with oversight of the 1985 NIH radioepidemiological tables report (NRC, 1984) objected to the use of the term "probability of causation," or "PC," for the ratio,

$$PC = \frac{\text{Risk due to radiation exposure}}{\text{Baseline risk} + \text{risk due to radiation exposure}}$$

$$= \frac{\text{excess relative risk}}{1 + \text{excess relative risk}}.$$

The NAS committee pointed out that a negative ERR would result in a negative "probability" (a defect easily remedied by specifying boundary conditions for PC) and, more seriously, that the ratio applied to populations and not individuals and could not be interpreted as the probability that a given cancer was caused by a given radiation exposure. They recommended using the term "assigned share" as a more appropriate term, because the computed quantities "are not probabilities in the usual sense and are truly properties of the group to which a person belongs, but in practice are assigned to the person for purposes of compensation." The present working group is sympathetic to this view and is in large part guided by it.

C. Methodology used in the 1985 report

1. **Data sources.** Baseline rates were taken from U.S. cancer incidence data for 1973-81 (SEER, 1984), by sex but not by race, and averaged over time . Site-specific average excess rates were taken from the 1980 report of the NAS/NRC Committee on the Biological Effects of Ionizing Radiation (BEIR III) (NAS, 1980, Tables V-14 and V-16) and from other sources, as shown in Table II.C.1. Lymphoma, multiple myeloma, and cancers of the prostate gland, uterus and cervix, testis, and brain specifically were not covered, because of insufficient information and lack of a statistically significant dose response. Chronic lymphocytic leukemia (CLL) was considered to be unrelated to radiation exposure.

Table II.C.1. Cancer sites covered by the 1985 tables report.

Site/cancer	Source of coefficients	Comments
Leukemia	BEIR III	Absolute risk coefficient for total leukemia multiplied by 0.68 for AL, 0.32 for CGL
Bone and joint	BEIR III	Injected 224-Ra only

Salivary gland	Survey of published results (Land, 1984)	Exposure ages 0-14 only
Esophagus	BEIR III	
Stomach	BEIR III	
Colon	BEIR III	Exposure ages 20+ only
Liver	BEIR III	Exposure ages 20+ only
Pancreas	BEIR III	Exposure ages 20+ only
Lung	Low-LET radiation: Kato & Schull, 1982; high-LET radiation, Jacobi et al, 1987	Exposure ages 10+ only
Breast	Tokunaga et al, 1987	Linear dose response assumed; no effect of fractionation or protraction of dose
Kidney & bladder	BEIR III	Exposure ages 20+ only
Thyroid gland	LSS incidence study (Parker et al, 1973)	Linear dose response assumed; no effect of fractionation or protraction of dose

2. Dose-response models. Based on a review of the experimental and epidemiological literature, a specific linear-quadratic model was assumed for all of the sites tabulated above, with the exception of breast and thyroid gland, for which linearity was assumed. The linear-quadratic model for a single, acute exposure to sparsely ionizing radiation (low-LET, for low linear energy transfer) was that preferred by the BEIR III committee (NAS 1980, equation V-10),

$$\text{excess risk} = \alpha\,(D + D^2/1.16),$$

where D is dose in Gy and α depends upon site, age at exposure, and sex. The value of α was equal to the corresponding linear-model risk coefficient from BEIR III or other source, divided by 2.5. Excess risk associated with a chronic exposure, or with exposure to densely ionizing (high-LET) radiation, was assumed to be linear in dose, with coefficient α. Different exposures were considered to be additive in effect; that is, excess risks associated with radiation exposures at different times were calculated separately and summed.

3. Minimal latent period and distribution of risk over time following exposure. For leukemia and bone cancer, radiation-related risk was assumed to be distributed lognormally over time following exposure, with a minimal latent period of 2 years. The lognormal distributions differed by cancer type and subtype and (for acute leukemia) by age at exposure, and were obtained by fitting original data. For other cancers, excess risk was assumed to be proportional to age-specific baseline risk (i.e., ERR was assumed to be constant) beginning 10 years after exposure; it was further assumed that there was no risk up to 5 years following exposure, and that ERR increased from zero at 5 years to its full value at 10 years according to a symmetric, S-shaped cubic polynomial function of time.

4. Dependence of excess risk on sex and on age at exposure. Following BEIR III, risk estimates were given separately by sex and age at exposure categories, regardless of statistical significance for these factors. Original estimates were in the form of excess (absolute) risk per unit dose, by sex and interval of age at exposure, averaged over a follow-up time of 5-26, 10-30, 10-33, 10-34, or 10-35 years, depending upon site; this corresponded to the data sets on which the estimates were based. Original estimates were converted to dose-specific ERR by dividing estimated excess risk by baseline risk, i.e., obtained as the lifetable-weighted average of age-specific SEER rates (SEER, 1997) over the same follow-up period. Thus, for sites where the excess risk estimate was based on Japanese A-bomb survivor data, and where U.S. and Japanese baseline rates differ, it was assumed that absolute risks, and not relative risks, averaged over the period of observation, were the same in the two populations.

5. Modification of ERR by other exposures and/or by host factors. The question of host factor modification was not addressed explicitly. Modification by other exposures was discussed generally, but specific recommendations were made only for tobacco smoking, in the case of lung cancer, and for radiation exposures other than those at issue. Different radiation exposures were treated as additive in effect, as discussed in II.C.1 above. Thus, the excess cancer rate corresponding to a second exposure was assumed to be independent of the excess cancer rate corresponding to an earlier exposure. Smoking and low-LET radiation were also considered to be additive in effect with respect to lung cancer causation, that is, the radiation-related excess rate was assumed to be independent of smoking history. Thus, a smoker would have a lower excess relative risk associated with exposure than an otherwise similar nonsmoker, because the nonsmoker's baseline rate was smaller. However, smoking and alpha radiation from inhaled radon decay products were considered to be multiplicative in effect, i.e., computation of ERR for radon exposure did not depend upon smoking history, since excess risk due to radiation and baseline risk were assumed to be proportionally affected by smoking history.

D. Uncertainty

Sources of biased and unbiased uncertainties, and propagation of errors, were extensively discussed in Chapter VII of the 1985 report. Biased uncertainties included overestimation of (absolute) risk 5-14 years following exposure, and underestimation associated with use by the BEIR III committee (NAS, 1980) of the T65D dosimetry system (Kerr,1979) for estimating dose-specific risk among A-bomb survivors. (By 1983-84 it was clear that T65D was going to be replaced, but the new system, DS86 (Roesch, 1987), was not yet in place.) Unbiased uncertainty pertained to the use of baseline rates based on the entire region covered by the SEER registry, modeling of risk as a function of age at exposure, assumptions about dependence of risk on time following exposure, and assumptions about the curvature of the linear-quadratic dose-response curve estimated in BEIR III. Other sources of uncertainty were also discussed, but only those just noted were taken into account in computing combined uncertainty, represented by a geometric standard deviation value and a bias correction factor, for different cancer sites and years following exposure. The emphasis of the report was on point estimates; recommendations were given for modifying tabulated AS values to account for bias and uncertainty.

III. Reasons for update

A. New data, new findings

The original NIH report was written in 1984, and based on data available at that time. Site-specific estimates of excess absolute risk (excess cases per 10^6 persons per year per rad), by interval of age at exposure, were obtained from the BEIR III report (NAS, 1980), which relied largely on A-bomb survivor mortality data for 1950-74 but also on other studies. The NIH report also used more recent risk coefficients from the A-bomb survivor Life Span Study (LSS) mortality report for 1950-78 (Kato&Schull, 1982) and site-specific, incidence-based studies of leukemia (Ichimaru,), thyroid cancer (Parker, 1974, Ishimaru, personal communication), and female breast cancer (Tokunaga, 1984) in the same population. To a lesser extent, the report surveyed studies of cancer mortality in British patients given therapeutic radiation for ankylosing spondylitis (1981), lung cancer among Czech, Canadian, Swedish and U.S. uranium miners (Jacobi, 1984), thyroid cancer in patients given x-ray epilation for treatment of tinea capitis (Ron and Modan, 1980, 1984), breast cancer among women given medical x rays (Boice, 1977, Shore, 1977), bone sarcoma among German patients treated for benign disease with injected radium (Mays, 1983), and estimates of salivary gland cancer risk in various irradiated populations (Land, 1984).

In the succeeding 15 years, the dose reconstruction system for the A-bomb survivors has been revised, and a large amount of new information has been obtained relating radiation exposure to subsequent cancer risk. For example, the number of cancer deaths among members of the cohort of atomic bomb survivors followed by the RERF in Japan increased from 3842 in 1950-74 (Kato and Schull, 1982) to 7827 in 1950-90 (Pierce, 1996). Much of the newer information pertains to cohort members exposed during the first and second decades of life: as these survivors reached ages at which cancer rates normally become appreciable, the newer data supported statistically stable risk estimates not obtainable previously. The same is in general true for other exposed cohorts that include persons exposed at young ages. In the original NIH report it was possible to estimate risk of radiation-related cancer following exposure before age 10 and at ages 10-19 for leukemia and cancers of the female breast, salivary gland, thyroid gland, and bone, while lung and stomach cancer risk estimates were available for exposure at ages 10-19. For other sites covered by the report (esophagus, colon, liver, pancreas, and urinary cancers), no calculations were done for exposure ages less than 20.

In addition, national and international committees have evaluated the newer data and used them for risk assessment (NAS, 1991, ICRP, 1991, UNSCEAR, 1988, 1994). Although none of these evaluations take account of the latest data, they are based on more recent data than BEIR III and

their existence and current use for radiation protection purposes underscores the fact that the estimates used in the 1985 NIH report are out of date. The risk estimates provided in ICRP Report 60 (1991) (based on the UNSCEAR 1988 report), in particular, are widely used and are generally higher than those in the BEIR III report.

B. New availability of risk data at the level of incidence.

Perhaps the most important recent development, however, has been a remarkable improvement, by the Radiation Effects Research Foundation (RERF) and its collaborators in Hiroshima and Nagasaki, of the Life Span Study (LSS) Tumor Registry to a high level of accuracy and efficiency (Mabuchi, 1994). The LSS registry draws on hospital records and physician notifications accessed by the local tumor registries of Hiroshima City, Nagasaki City, and Nagasaki prefecture, pathology and hematology records through the Hiroshima and Nagasaki tissue registries, and the Leukemia Registry developed in the late 1940s and early 1950s, as well as the virtually complete system of mortality notification and ascertainment of death certificate diagnosis that is the basis of the LSS mortality studies of atomic bomb survivors. In general, incidence data, when they can be obtained, are superior to mortality data because they capture information on cancers of low or delayed fatality and because they are based on diagnostic information that is more detailed and more accurate than death certificate data.

C. The use of the NIH report today is somewhat different from that contemplated at the time the report was written.

The circumstances of the legislation mandating the 1985 NIH report suggested that partial compensation for claims of radiation-related cancer might be made on the basis of assigned share estimates between 10% and 50%, whereas full compensation would apply for AS $\geq$ 50%. Thus, the main graphical displays in the report show computed, "best-estimate" AS values corresponding to organ doses of 1, 10, and 100 rad (0.01, 0.10, and 1.0 Gy), as a function of age at exposure and/or time following exposure, and the reader is referred to the chapter on uncertainty limits for instructions on how to compute them. In fact, the tort law concept of "at least as likely as not," corresponding to AS $\geq$ 50%, continues to dominate the language of claim adjudication, with the notable modification in some important applications that claims may be winnowed out only if there little or no reasonable doubt that the true value of the AS is less than 50%. For example, the Department of Veterans Affairs (VA) screens out claims for which the 99% upper limit for the AS is less than 50% (Dr. Neil Otchin, personal communication). This development suggests that any revision of the 1985 report should seek a more nearly complete expression of the scientific information related to risk of cancer following exposure to ionizing radiation, as it applies to particular cases. In other words, emphasis should be placed upon a

comprehensive expression of uncertainty, and one that is easily accessible to the user.

D. New attention to cancer sites whose association with radiation exposure is tenuous.

The cancers covered by the 1985 NIH report were those for which a statistically significant radiation dose response had been demonstrated in one or more major analyses. Statistical significance is equivalent to having a positive lower confidence limit, at a certain confidence level, for dose-specific excess relative risk, and therefore also for the AS. The list of cancers fitting this criterion is not greatly different today, but it is clearly possible for an upper uncertainty limit for the ERR to be greater than 1, and hence for the corresponding AS limit to be greater than 50%, even when the AS is not significantly greater than zero. Thus a wider range of cancer sites is of interest than that covered by the 1985 report.

E. New analytical approaches and ways of summarizing data

The 15 years since the 1985 NIH report have seen enormous advances in accessible computing power, particularly at the level of personal computers, and the development and refinement of statistical packages for risk analysis. An important consequence is that statistical modeling of radiation dose response and its modification by factors such as gender, age at exposure, time since exposure, age at observation for risk, smoking history, and reproductive history can be carried out far more quickly and easily than before. New analyses, tailored for particular applications like the subject of this report, are easily accomplished, especially since the important LSS mortality and incidence data are available from RERF on request from non-RERF scientists. These data, grouped to protect the privacy of individual survivors, are those used in the 1950-85 mortality report (Shimizu et al, 1990) and the 1994 incidence reports based on RERF Tumor Registry and Leukemia Registry data through 1987 (Thompson et al, 1994, Preston et al, 1994). The AMFIT algorithm for Poisson model regression, part of the Epicure statistical package (Preston et al, 1991), is particularly well suited for cohort-based analyses of radiation-related risk and has become closely identified with analyses of A-bomb survivor data in particular. These statistical approaches were used, for example, to develop the models used in the BEIR IV, V, and VI reports (NAS, 1988, 1990, 1999).

F. More attention to uncertainty and presentation of risk

The 1985 NIH report presented illustrative graphs of assigned share estimates, tables of coefficients for various components needed to compute assigned share, and algorithms for calculating assigned share from these coefficients for arbitrary values of radiation dose, age at exposure, and time following exposure. Statistical and other sources of bias and uncertainty were extensively discussed in a separate chapter, and estimates and algorithms were provided for

calculating "credibility limits" (based on statistical and subjective measures of uncertainty) for estimates of assigned share. In the intervening years, additional attention has been paid to quantification of uncertainty in applications to radiation-related risk, and new approaches for evaluating uncertainty have been developed (NAS, 1990, NCRP, 1996, 1997, EPA, 1999). It seems clear that considerations of uncertainty are central to radiation protection and adjudication of claims for compensation in cases of disease following radiation exposure. It is equally clear that the concept is complex and not easily applied by non-specialists, and would benefit from a more user-friendly approach as indicated by the following example:

The major U.S. government user of the NIH report is the Department of Veterans Affairs (VA) which in 1985 asked the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) of the Office of Science and Technology Policy, Executive Office of the President, to provide guidelines on how the NIH report might be used credibly to assist in adjudicating a veteran's claim of radiation injury. The Science Panel of CIRRPC interpreted the VA's charge as one of quantifying the likelihood that a specified "probability of causation" (assigned share) in the NIH report would not be exceeded, with an *a priori* chosen level of credibility (CIRRPC, 1988). Their solution was to tabulate, by type of cancer, gender, age at exposure, and other relevant factors, the organ doses at which the upper AS credibility limit was 50% ("as likely as not") at credibility levels 90%, 95%, and 99%, respectively. The solutions were proposed as possible screening doses for specific cancers, exposure ages and times following exposure. The screening procedure was biased toward ensuring that a marginal claim by an exposed veteran would not be rejected at this stage of consideration, and it was assumed that a claim not eliminated by this screening process would be adjudicated on its merits, taking into consideration the many factors that pertain to an individual claimant, including the AS value calculated according to the NIH report.

G. Availability of interactive computer programs as an alternative to tabular presentation

The tabular presentation of the 1985 report allowed users to look up tabulated coefficients appropriate to particular claims, and to calculate assigned share using these coefficients according to simple algorithms presented in the report. Increased computing power has made it possible to calculate assigned share and its uncertainty directly, for individual claims, from the particulars of exposure history, disease, and other relevant factors. This results in quicker, easier, and less error-prone computation, with tabular and/or graphical output options.

H. Use of organ-specific dose equivalent, in sievert (Sv)

The present report expresses organ-specific absorbed radiation dose in units of gray (1 Gy = 1

Joule per kilogram of tissue), instead of the previous unit used in the 1985 report, the rad (1 Gy = 100 rad; equivalently, 1 cGy = 1 rad), and equivalent dose, which incorporates different weighting factors for different types and energies of radiation, in units of sievert (Sv; 1 Sv = 100 rem, where the rem is the previously used unit). For low-LET radiation like gamma ray and x ray, dose and equivalent dose are numerically equivalent (e.g. 5 cGy = 5 cSv), but for high-LET radiation like neutrons or alpha particles, a given dose may correspond to many more units of dose equivalent, depending on the type of radiation and the dose level. In the present report, it is assumed that the starting point for calculations of AS are tissue-specific dose equivalent values expressed in Sv or cSv, using the appropriate conversion from tissue dose in Gy.

IV. Description of the Approach

A. Overview

1. Assigned Share

Assigned share (AS) for an individual who was exposed to radiation, and who has been diagnosed with a cancer thought to be related to such exposure, is given by

$$AS = ERR/(1 + ERR)$$

where ERR is the excess relative risk associated with the exposure(s) of interest. ERR is a function of radiation dose (possibly accumulated over a number of exposures), age(s) at exposure, type of cancer, age at diagnosis, gender, and other factors possibly related to baseline and/or radiation-related risk.

As previously mentioned (section II.B), the working group is sympathetic to the view expressed by the 1984 oversight committee report (NAS, 1984), that the ratio, called "probability of causation," or "assigned share" (which we prefer) applies to populations and not individuals and cannot, for lack of detailed information and the ability to understand its full implications, be interpreted as the probability that a given cancer was caused by a given radiation exposure. The working group views assigned share as an actuarial concept, useful for summarizing the existing scientific evidence bearing on the likelihood that prior radiation exposure might be causally related to cancer occurrence under various circumstances, and which may in fact be the best available information pertaining to a particular case. Similarly, a statistical life table is a useful device on which to base social contracts such as a life insurance contract. A life table is based on observed frequencies of deaths by age in a large population and, with detailed information, it is easy to define, and easier still to imagine, subgroups for which life-table predictions based on the larger population may perform poorly. Yet these departures do not detract from the practicability of basing decisions about annuities, insurability, and insurance rates on life table predictions in the absence of such detailed information.

2. Criticisms by Greenland and others

The present working group has considered criticisms of the AS approach by Greenland and colleagues (Greenland, 1988, 1999; Robins, 1989a, 1989b; Beyea, 1999), who argue that AS is a logically flawed concept, subject to substantial bias and therefore unsuitable as a guide to adjudication of compensation claims in cases of possibly radiation-related cancer. Their argument is based largely on the possibility that radiation exposure might accelerate the time of appearance of a cancer that, in the absence of exposure, would have occurred later. The working

group has concluded that the practical effect of such events is unlikely to be great enough to affect the viability of the AS approach.

In support of this conclusion, the working group notes that heavily-irradiated populations that have been studied extensively, like the higher-dose survivors of the atomic bombings of Hiroshima and Nagasaki, have experienced increases in cancer risk rather than a temporal redistribution of risk over their lifetimes. The phenomenon of radiation-related "acceleration of risk," observed in highly sensitive inbred animal strains with very high lifetime tumor risks in the absence of exposure, appears to be an artifact in that a radiation-related increase in the number of tumors per animal is observed as an acceleration in time to first observed tumor -- the first of many is likely to appear before the first of relatively few (Guess and Hoel, 1977). In any case, the influence on radiation-related risks in general populations of highly sensitive population subsets is thought to be relatively minor (ICRP, 1999). At the cellular level, ionizing radiation is generally believed to be more effective as a cell killer than as a cell mutator (Hall, 1994), and cancer cells are believed to be more vulnerable than normal cells to radiation-induced cell killing (this is the basis for radiation-based cancer therapy). It is of course theoretically possible that a particular cell, having already gone through one or more stages in the multi-stage process of carcinogenesis, might be moved farther along in the process by a radiation event that accomplishes what some other event would otherwise have accomplished later. Given the very large number of potential target cells in the human body or in a particular organ or tissue, however, it is reasonable to conclude that the carcinogenic effect of radiation in an individual or a population is dominated by interactions with cells not already destined to develop into cancer.

The acceleration hypothesis does not play a major role in current models of radiation-related risk in general populations, and particularly not in models directed at radiation protection. The scientific consensus on which reports like the current one are based is an evolving process, based on imperfect knowledge. The working group sees no reason why that consensus should not be used, at any given time, as a guide for adjudication of claims as well as for radiation protection.

3. Emphasis on uncertainty analysis

New emphasis is placed on uncertainty analysis (NCRP, 1996), specifically, estimating an uncertainty distribution for the ERR (and associated AS), as opposed to a single point estimate. ERR is expressed as the product of several factors, assumed to be independent. Each factor is uncertain, and is specified by an uncertainty distribution. The specified uncertainty distributions depend to some extent on subjective judgments by expert committees and by the authors of this report. The overall uncertainty distribution of the desired ERR is obtained by Monte Carlo simulation. These simulations involve sampling from the uncertainty distributions for each of

the factors (or sources) included, and are similar to those conducted by the Environmental Protection Agency (EPA,1999) and the National Council on Radiation Protection and Measurement (NCRP,1997). A computer program, here called IREP (for interactive radio-epidemiological program), has been developed to conduct these simulations individually for any desired application, taking account of specific characteristics of both the exposure and of the exposed individual.

The sources of uncertainty that are included are listed below, with details given in the sections that follow and in the appendices.

1. Sampling variability in the estimated ERRs. Statistical analyses of A-bomb survivor cancer incidence data were performed to estimate the ERR and its associated statistical uncertainty for each type of cancer. Dose response was assumed to be linear for solid cancers, after dose-response analyses found no evidence of departure from linearity. For leukemia, dose response was assumed to be linear for densely ionizing radiation such as neutrons and alpha particles, and for sparsely ionizing radiation (e.g., gamma ray, x ray) delivered at low dose rates; but quadratic for acute exposures to sparsely ionizing radiation. For some cancer types, statistically significant improvements in fit were obtained by modeling dependence of dose response on sex, age at exposure, age at diagnosis, and/or time since exposure. For these cancers, sampling variability reflects statistical uncertainty about the estimated dependency of dose response on these additional factors. Details are given in Section IV.D and Appendix C.

2. Correction for random and systematic errors in A-bomb survivor dosimetry. Risk estimates are adjusted for random errors in the doses assigned to individual survivors, and also to several potential sources of systematic bias in these doses. The latter include systematic underestimation of gamma rays for Hiroshima survivors, uncertainty in the weighting factor for neutrons, and uncertainty in the neutron component of the total dose. Details are given in section IV.E.

3. Extrapolation of risk from sparsely ionizing radiation to low doses and dose rates. Doses received at low doses and dose rates are adjusted by a factor known as the Dose and Dose Rate Effectiveness Factor (DDREF). The treatment of the uncertainty in this factor is described in Section IV.F and Appendix C.

4. RBE for high-LET radiation exposure. Densely ionizing radiation, with a high level of energy transfer per length of radiation track in tissue (high linear energy transfer, or high-LET for short), such as protons, neutrons, and alpha particles and other heavy ions, generally has a greater biological effect per unit dose than low-LET radiation such as gamma ray, x ray, and beta particles. For radiation protection purposes, high-LET radiation dose is weighted by an

appropriate RBE factor (for relative biological effectiveness); the resulting weighted dose, sometimes referred to as dose equivalent, is used when applying risk coefficients derived from studies of populations exposed mainly to low-LET radiation. RBE may depend upon the type of radiation and the level of dose, and is an uncertain quantity derived from observational data. Treatment of this uncertainty is discussed in Section IV.G.

5. Transfer of risk estimates form A-bomb survivors to a US population. Baseline risks for many cancers differ substantially for Japanese and US populations, and there is considerable uncertainty about how risk estimates derived from observations on an exposed Japanese population should be applied to an exposed US population. The treatment of this source of uncertainty is described in Section IV.H.

6. Modification by smoking history. Tobacco smoking and, to a lesser extent, exposure of nonsmokers to side stream tobacco smoke are powerful risk factors for lung cancer, especially, and a number of other cancers as well. Studies of uranium miners suggest that risk of radiation-induced lung is increased among smokers to a greater extent than among non-smokers, but that this increase is somewhat less than the increase associated with smoking alone (NAS, 1999). The interaction between radiation exposure and smoking history is discussed in Section IV.I.

The following additional sources of uncertainty have been considered by others, but are not evaluated here.

1. Diagnostic misclassification in A-bomb survivor data. Both the NCRP (1997) and EPA (1999) uncertainty evaluations were based on mortality data, for which diagnostic misclassification is a more serious problem than for the incidence data used for this report. Also, the present report focuses on specific cancers, and diagnostic accuracy may depend on the cancer type. Although there is undoubtedly uncertainty resulting from diagnostic misclassification, it would be very difficult to quantify, and it did not seem likely that this uncertainty would be large relative to many of the other sources considered.

2. Extrapolation of risk beyond the time period covered by data. The focus of NCRP Report 126 (1997) was lifetime cancer mortality risk associated with radiation exposure, and the report specifically treated uncertainty about extrapolation of risk beyond the period of observation for risk. The concern was that the A-bomb survivor mortality data for 1950-1985 represented follow-up only until 40 years after exposure, whereas those data were being used to estimate lifetime risk for persons exposed at various ages including children whose expected remaining lifetime when exposed was 50, 60, 70, or more years. The NCRP report included a factor whose uncertainty contributed 6.7% of the overall uncertainty to *lifetime* mortality risk for a population

of all ages at exposure, and 0.5% for a working population 20-65 years of age at exposure.

The present report is subject to the same problems of projection of risk beyond the period of observation. However, the vast majority of claims for which the report might be relevant are expected to pertain to adult exposures, for which such projection contributes little compared to other sources of uncertainty. Thus, no special provision was made for uncertainty of extrapolation beyond the period of observation. On the other hand, trends in time since exposure and age at cancer diagnosis, which address some of the same issues, were specifically included in the set of variables used to model radiation-related risk for different kinds of cancer, and were retained in the model as appropriate on statistical grounds.

B. Source of data

Although much new information on radiation-related risk in human populations has been published in the 15 years since the 1985 NIH report was prepared, the present report relies primarily on analyses by the Working Group of A-bomb survivor incidence data. The approach involves direct calculation of risk estimates and their statistical uncertainties from original data, in this case from the RERF Tumor Registry for 1958-87 (Thompson et al, 1994), the RERF Leukemia Registry for 1950-1987 (Preston et al, 1994), and site-specific studies of salivary gland cancer (Land et al , 1996) and female breast cancer (Land, personal communication) in the LSS cohort. Thyroid cancer receives a more widely-based approach, involving a new analysis of the original thyroid cancer data from the international, pooled study of Ron et al (1995).

C. Choice of cancer types and approach to cancer types (each type considered individually)

Adjudication of compensation claims for possibly radiation-related cancer is usually specific to organ site and often to histological type. Sites for solid tumor incidence data from the RERF Tumor Registry are specified in Table IV.C.1, and sites for hematopoietic cancers from the Leukemia Registry are shown in Table IV.C.2. Calculations were completed for individual organ sites and for broader groups (all leukemia except the chronic lymphocytic type, and for cancers of the urinary system); the broader groups are intended to provide some basis for adjudicating claims for organ sites not specifically covered.

Chronic lymphocytic leukemia (CLL) was specifically excluded from the risk calculations because of a lack of data on which to base an estimate. CLL is almost absent among Japanese generally and among the A-bomb survivors in particular (Parkin, 1997, Preston, 1994), but occurs frequently in Western populations, especially at older ages (Parkin, 1997). It has not, however, been associated with radiation exposure in studies of irradiated Western populations (NAS, 1990). Malignant melanoma also was excluded, because no convergent estimate could be

obtained on the basis of the limited data available. Thus, there was no evidence that it is associated with radiation exposure but, also, no persuasive evidence that it is not. Non-melanoma skin cancer was not included because, although risk, and risk of basal cell carcinoma in particular, have been found to be associated with radiation dose in the A-bomb survivor population (Thompson et al, 1994, Ron et al, 1998) and in persons irradiated as children in connection with treatment for ringworm of the scalp (Shore, 1984), it is not a reportable illness in the United States and reliable population rates are lacking.

Calculations were performed for the following cancers which were not significantly associated with radiation dose: cancers of the oral cavity and pharynx as a group, rectum, gall bladder, pancreas, residual gastric, nasal, larynx and residual respiratory, female genital cancers as a group, uterus not otherwise specified (NOS), uterine cervix, prostate, testes and residual male genital, renal pelvis, lymphoma, and multiple myeloma. Modifiers of dose response included in the fitted model, such as gender, age at exposure, attained age, and time following exposure, are presented in Table IV.C.1 for these cancers and for others whose associations with radiation dose are more clearly established.

Table IV.C.1 Solid cancer sites covered by the present report, and dose-response modifiers included in the risk estimate and uncertainty analysis.

Cancer site[1]	ICD-O codes	Cancer cases			Modifiers in fitted model[2]
		≥10 mSv	< 10 mSv	Total	
Oral cavity and pharynx[3]	140-149	64	68	132	none
Salivary glands[4]	142	18	11	29	not fitted[5]
Parotid gland	142.0	7	6	13	none
Other salivary glands	142.1-9	11	5	16	none
Digestive system	150-159	2355	2442	4797	not fitted[5]
Esophagus	150	84	101	185	g
Stomach	151	1305	1353	2658	g, e
Colon	153	223	234	457	a
Rectum	154	179	172	351	none
Liver	155.0	283	302	585	g, e
Gallbladder	155.1, 156	143	152	295	none
Pancreas	157	122	118	240	none
Other digestive	152, 158, 159	16	10	26	none
Respiratory system	160-165	528	499	1027	not fitted[5]
Nasal cavity	160	34	21	55	none
Larynx and other respiratory	161, 163-165	45	55	100	none
Trachea, bronchus, and lung	162	449	423	872	g
Malignant melanoma	173	6	7	13	not fitted[6]
Female breast[7]	174	452	514[8]	966	e
Female genital[3]	179-184	430	461	891	none

Uterus NOS	179	47	39	86	none
Uterine cervix	180	265	288	553	none
Uterine corpus	182	37	48	85	not fitted[6]
Ovary	183	66	67	133	none
Other female genital	181, 184	15	19	34	not fitted[6]
Male genital	185-187	74	86	160	not fitted[5]
Prostate gland	185	61	79	140	none
Other male genital	186,187	13	7	20	none
Urinary system[3]	188-189	172	153	325	g
Bladder	188	115	95	210	g
Kidney	189.0	34	39	73	g, a
Renal pelvis and ureter	189.1, 189.2	14	14	28	none
Nervous system	191, 192	69	56	125	none
Thyroid gland[9]	193	129	96	225	e

[1]Except as noted, information based on Thompson et al, 1994.

[2]g = gender, e = age at exposure, a = attained age, t = time following exposure

[3]Use group estimate for cancers in this group for which site-specific estimates are not provided.

[4]Salivary gland data from Land et al, 1996.

[5]Use site-specific estimates.

[6]Fitting process did not converge; use group estimate.

[7]Breast cancer data from C. Land, personal communication.

[8]Includes non-exposed cases.

[9]Thyroid cancer data from Ron et al, 1996, reanalyzed for this report.

Table IV.C.2 Hematopoietic cancers included in the present report, and dose-response modifiers included in the risk estimate and uncertainty analysis.

Cancer type	ICD-9 codes	Cancer cases			Modifiers in fitted model[1]
		≥10 mSv	< 10 mSv	Total	
Leukemia, all types (except chronic lymphocytic leukemia)	204-208, minus 204.1	143	90	233	g, e, t
Acute myelogenous leukemia	205.0	60	43	103	t
Acute lymphocytic leukemia	204.0	24	9	33	t
Chronic myelogenous leukemia	205.1	41	17	58	g, t
Multiple myeloma	203	31	29	60	none
Lymphoma	201-202	86	105	191	none

[1]g = gender, e = age at exposure, a = age at diagnosis, t = time following exposure

D. Estimation of risk coefficients and their statistical uncertainties

General models. Site-specific baseline incidence was modeled as a function of gender, city of exposure (Hiroshima or Nagasaki), year of birth, calendar time (where indicated), and age at observation for risk (attained age), as discussed in Thompson et al (1994) and Preston et al (1994). Default dose-response models were linear (proportional to dose equivalent D in Sv, henceforth called "dose" for brevity) for solid tumors and for leukemia associated with exposure to high-LET radiation or low-LET radiation delivered at low dose rates (chronic exposure), and linear-quadratic for leukemia associated with acute exposure to low-LET radiation. The quadratic model was set to have equal contributions of the dose and dose-squared terms at 1 Sv (proportional to $D+D^2$). Fitting a general linear-quadratic (proportional to $D+\zeta D^2$) resulted in no statistically significant evidence of nonlinearity for solid tumors or for lymphoma and multiple myeloma among hematopoietic cancers. For leukemia generally (all types except chronic lymphocytic (CLL)) and for acute myelogenous, acute lymphocytic, and chronic myelocytic leukemia in particular, various estimates of ζ were obtained, depending on the type of leukemia, that were greater than zero. However, since all these estimates were statistically consistent with the default value $\zeta=1$, the final models for leukemia and its subtypes were based on $\zeta=1$.

In terms of potential modifying factors such as gender (g), age at exposure (e), attained age (a), and time since exposure (t), the fitted model was

$$ERR(D,g,e,a,t) = \alpha f(D) \exp(\beta g + \gamma e + \delta a + \epsilon t),$$

where $f(D) = D$ for most cancers and $f(D) = D+D^2$ for leukemia associated with acute exposure to low-LET radiation, where α, βg, γ, δ, and ϵ are unknown parameters. Parameter α was estimated from the data; parameters βg, γ, δ, and ϵ were estimated from the data or, if they made no significant contribution to improvement of the fit of the model to the data, set to zero. (Note that at least one of the parameters γ, δ, and ϵ must always be set to zero because t = a-e.)

Uncertainty about all unknown parameters is reflected in uncertainty about ERR. The parameter α corresponds to the excess relative risk when D=1 (or $D+D^2=1$), g=0, e=0, a=0, and t=0. Thus (for example) the estimated ERR_{1Sv} for leukemia (all types except CLL) among females exposed at age 20 and observed at age 47 (27 years following exposure) can be obtained by setting $\delta=0$ and assigning values to g, e, and t as follows: g = 0 and 1 for females and males, respectively, e = exposure age - 20, and t = time since exposure - 27. The statistical uncertainty distribution of the resulting estimate is described by the profile likelihood distribution of the fitted parameter α (Figure IV.D.1). Other examples are shown in Figures IV.D.2 (stomach and colon) and IV.D.3 (thyroid and liver).

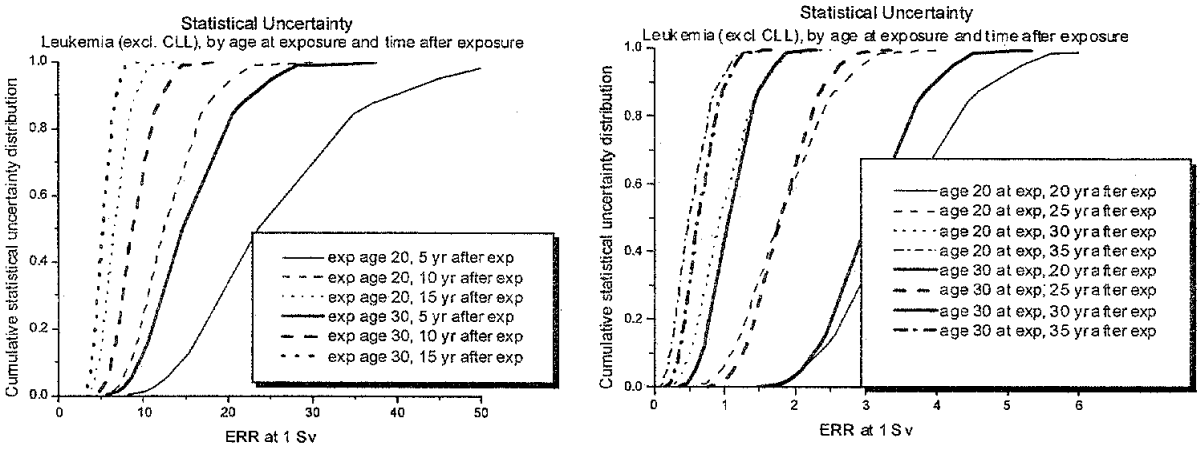

Figure IV.D.1. Statistical uncertainty distributions for leukemia (all types except chronic lymphocytic leukemia), by age at exposure (20 and 30) and time following exposure (5-35 yr).

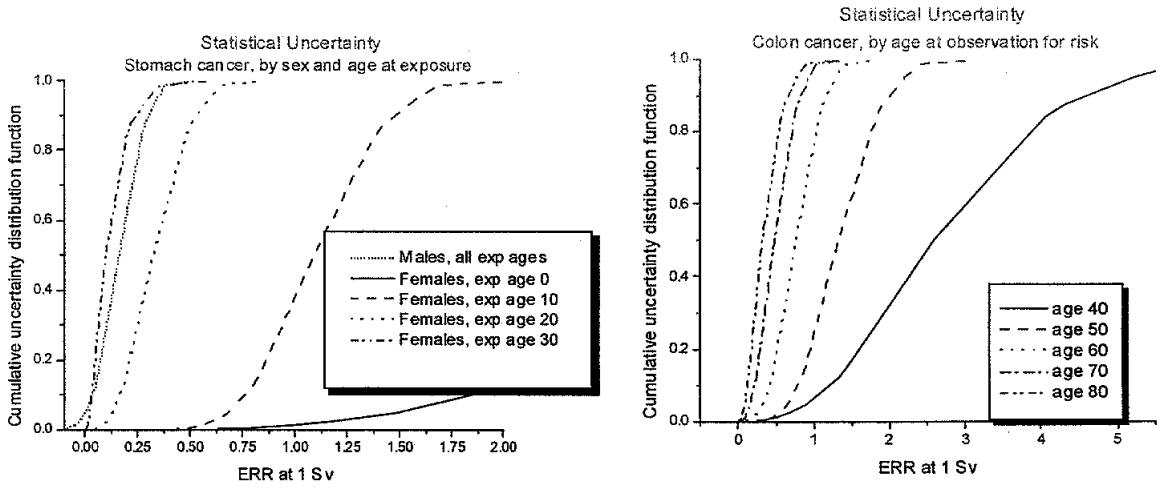

Figure IV.D.2. Statistical uncertainty distributions for stomach cancer (by gender and age at exposure) and colon cancer (by age at observation for risk)..

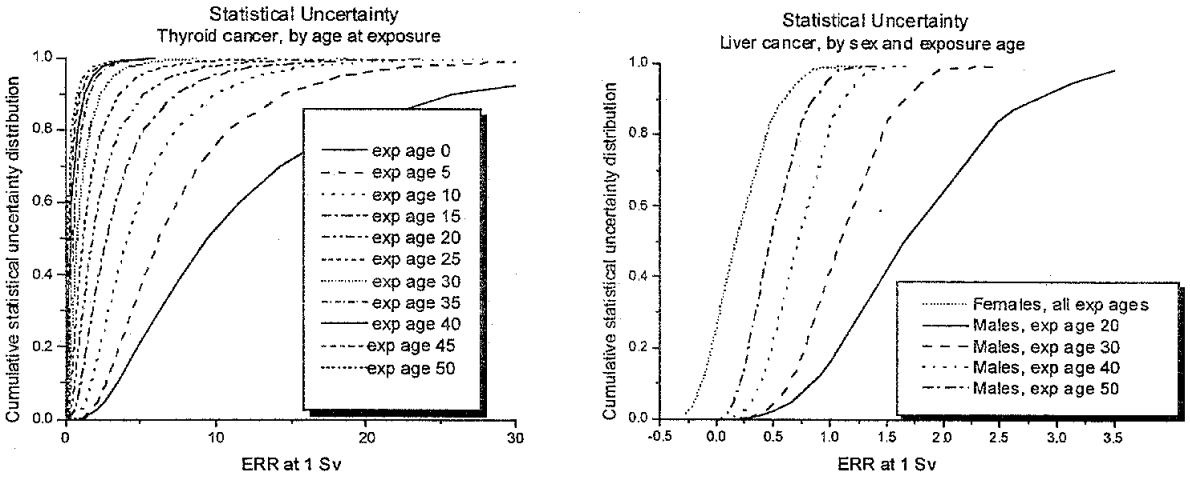

Figure IV.D.3. Statistical uncertainty distributions for thyroid cancer (by age at exposure) and liver cancer (by sex and, among males, age at exposure).

Thyroid cancer. Thyroid cancer risk, estimated from the combined analysis data used by Ron et al (1995), required special handling because the data were from 6 different study populations (treating Hiroshima and Nagasaki survivors separately) with possibly different baseline and excess risks. The final model (there was no statistically significant dependence on gender or attained age) was

$$ERR(D,e) = D \exp(\theta_1 I_1 + ... + \theta_6 I_6 + \beta e),$$

where I_1, ..., I_6 are indicator functions for the 6 study populations and where θ_1, ..., θ_6 are assumed to be normally distributed random variables with common mean θ. Parameter estimates θ_1, ..., θ_6 and β, and their estimated asymptotic covariance matrix, were obtained by Poisson regression (Hirosoft). The parameter estimate θ was calculated as the mean of θ_1, ..., θ_6, weighted by the inverse of their estimated covariance matrix Σ. The off-diagonal elements of Σ were positive, indicating that θ_1, ..., θ_6 were positively correlated.

The variance of the estimate θ was adjusted for nonhomogeneity of study populations by the method of DerSimonian and Laird (1986) for meta-analysis of clinical trials, as adapted by Ron et al (1995). The method assumes statistical independence among estimates obtained from different studies, a condition that was not strictly met in the present analysis because a common age-at-exposure parameter was used for the several studies. Since individual study estimates were positively correlated, use of the method is likely to have overestimated the variance of θ.

The uncertainty distribution for θ was assumed to be normal with mean and variance equal to θ

and its estimated (adjusted) variance, respectively. ERR_{1Sv} for any given exposure age e_0 was estimated as the exponential of θ, calculated with e = exposure age - e_0, and was assumed to have a lognormal uncertainty distribution.

E. Correction for random and systematic errors in A-bomb survivor dosimetry

Our treatment of random and systematic errors in A-bomb survivor dosimetry was based mainly on the treatment described in Chapter 3 of NCRP Report 126 (1997), and the reader is referred to this material for details. The NCRP approach was also used by the EPA (1999). For each source of uncertainty, a bias factor with an uncertainty distribution was specified, and this factor was used to correct ERR estimates based on the A-bomb survivor data. Sources of bias and uncertainty that were evaluated by the NCRP are as follows:

1) Uncertainty in the magnitude of random errors in the doses of individual survivors, called R_E in NCRP Report 126, contributed differently to biased uncertainty for solid cancers and the leukemias, for which the forms of the dose response were linear and linear-quadratic, respectively. Unlike the NCRP report, the present report is concerned with individual cancer sites and must consider the two cases separately: uncertain bias correction factors $1+F_L(R_E)$ and $1+F_Q(R_E)$ for cancers with linear and linear-quadratic dose responses, respectively. Pierce et al (1990) recommended a lognormally-distributed random error in individual dose estimates with geometric mean (GM) = 1 and geometric standard deviation (GSD) = exp(0.35), corresponding to an upward correction in estimated risk of 9.0% for solid cancers and 5.6% for leukemia, with essentially no effect on the variability of the corrected risk estimates. There is, however, some uncertainty corresponding to the assumed GSD of the lognormally-distributed random error in dose estimates: the corresponding upward corrections are 6.8% and 4.3% for solid cancers and leukemia, respectively assuming log GSD = 0.30, and 11.4% and 7.2% assuming log GSD = 0.40. If we consider 0.30 and 0.40 to correspond to the 10^{th} and 90^{th} percentiles of an uncertainty distribution for log GSD, and consider that random error in dose assignment can only bias estimated risk downward, it seems appropriate to assume that $F_L(R_E)$ and $F_Q(R_E)$ are lognormal with GM=8.8% and 5.56%, respectively, with common GSD=1.22 (i.e., LN(8.8%, 1.22)) and LN(5.56%, 1.22)).

2) Uncertainty in the appropriate choice of neutron RBE in analyzing A-bomb survivor data, denoted N_R in NCRP 126 with error factor $F(N_R)$ distributed according to a triangular distribution with minimum 0.9, most likely value 1.0, and maximum 1.1 (i.e., triangular(0.9, 1.0, 1.1)).

3) Uncertainty due to systematic bias in gamma dose estimates, denoted D_γ in NCRP 126 with error factor $F(D_\gamma)$ distributed as triangular(1.0, 1.1, 1.4).

4) Uncertainty due to systematic bias in neutron dose estimates in Hiroshima, denoted D_n in NCRP 126 with error factor $F(D_n)$ distributed as triangular(1.0, 1.1, 1.3).

The overall error factors for random and systematic errors in dosimetry are

$$F_L(D) = (1+F_L(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for solid tumors and

$$F_Q(D) = (1+F_Q(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for leukemia. The uncertainty distributions for $F_L(D)$ and $F_Q(D)$, expressed in percent, correspond reasonably well to normal distributions: N(83.2, 8.36) and N(80.7, 8.05), respectively.

F. Dependence of risk on dose and dose rate for low-LET radiation

Radiations of different quality differ with respect to the shape of the dose-response function for cancer risk. Risk per unit dose of radiations of high linear energy transfer (LET), such as neutrons, alpha particles, or heavy ions, tend to be the same (or greater) at low compared to high doses, whereas for low-LET radiations, such as gamma ray, electrons, x ray, or beta particles, risk per unit dose is thought to be lower at low dose levels. Evidence for a lower risk per unit dose of low-LET radiation at low (compared to high) dose levels comes mainly from experimental radiobiology, much of it involving outcomes other than carcinogenesis (NCRP, 1980). Inferences about the shape of the dose-response relationship based on epidemiological studies of cancer, on the other hand, tend to be determined by data in the middle and high dose ranges, i.e., 0.1-1.0 Gy and 1.0 Gy and higher. For solid cancers, generally, there is little persuasive epidemiological evidence of nonlinearity of dose response, whereas for leukemia there is good evidence of positive curvature. The quadratic dose-response model for leukemia used here corresponds to a risk at 0.01 Gy (1 cGy) that is only 0.5% as high as the risk at 1 Gy, or half as high per unit dose. Linear-model risk coefficients may be reduced by a dose and dose-rate effectiveness factor (DDREF) for estimating risks at low doses and low dose rates. The International Commission on Radiological Protection (ICRP, 1991) recommended a DDREF of 2 for purposes of radiation protection, a value roughly consistent with the default quadratic dose-response model used here for leukemia. The ICRP recommendation is also accepted by the NCRP (1993). In their most recent discussion of the application of DDREF, the United Nations Subcommittee on Effects of Atomic Radiation (UNSCEAR, 1993) recommended that the chosen DDREF be applied to chronic exposures (dose rates less than 6 mGy per hour averaged over the first few hours) and to acute (high dose rate) exposures at total doses less than 0.2 Gy, a recommendation that was subsequently adopted by the EPA (1999). However, such an abrupt transition seems unrealistic in view of observed linearity

of dose response for cancer incidence and mortality among acutely exposed A-bomb survivors, down to and including values below 0.2 Gy (Thompson et al., 1994, Pierce et al., 1996). Also, continuous uncertainty distributions for DDREF, including values as low as one and as high as five, have been used by NCRP (1997) and EPA (1999) for calculations of lifetime risk of all cancer types combined (Figure IV.F.1).

In the present report, ERR is estimated as a function of radiation dose, and modified according to exposure rate (acute or chronic) by application of an uncertain DDREF. The DDREF is applied to all chronic exposures whereas, for an acute exposure, the DDREF is phased in as dose is decreased, beginning at an uncertain reference dose less than 0.3 Sv and decreasing smoothly to the value appropriate for chronic exposure. Fractionated acute exposures separated by 5 hours or more are treated as separate exposures; thus, the DDREF is applied to each fraction and their estimated effects on risk are added together. A discrete, subjective probability distribution of DDREF ($DDREF_{chronic}$), based on the NCRP and EPA models (Figure IV.F.1), is applied to most non-leukemia cancers for chronic exposures and to acute exposures at very low doses. The distribution assigns subjective probability weights of 20%, 20%, 32%, 16%, 8%, and 4% to $DDREF_{chronic}$ values 1, 1.5, 2, 3, 4, and 5, respectively (Figure IV.F.2). Both the mean and median of this distribution are close to 2. The evidence for a linear dose-response is especially strong for cancers of the thyroid gland and female breast (Ron et al, 1995, Tokunaga et al, 1994); for these cancers, the distribution assigns weights of 40%, 23%, 23%, 10%, 4% and 0%, respectively, to the specified array of values for $DDREF_{chronic}$. The mean and median of this distribution are, respectively, 1.7 and 1.5.

For an *acute* exposure, the DDREF ($DDREF_{acute}$) is modeled as a random quantity that approaches $DDREF_{chronic}$ as dose decreases to zero. Between zero and an uncertain reference dose, D_L (between 0.03 and 0.3 Gy), $DDREF_{acute}$ increases smoothly from $DDREF_{chronic}$ at zero dose to 1 at D_L and above, according to a logistic function of dose (Figure IV.F.3). The uncertainty in the reference dose D_L is expressed as a log-uniform distribution (Figure IV.F.4).

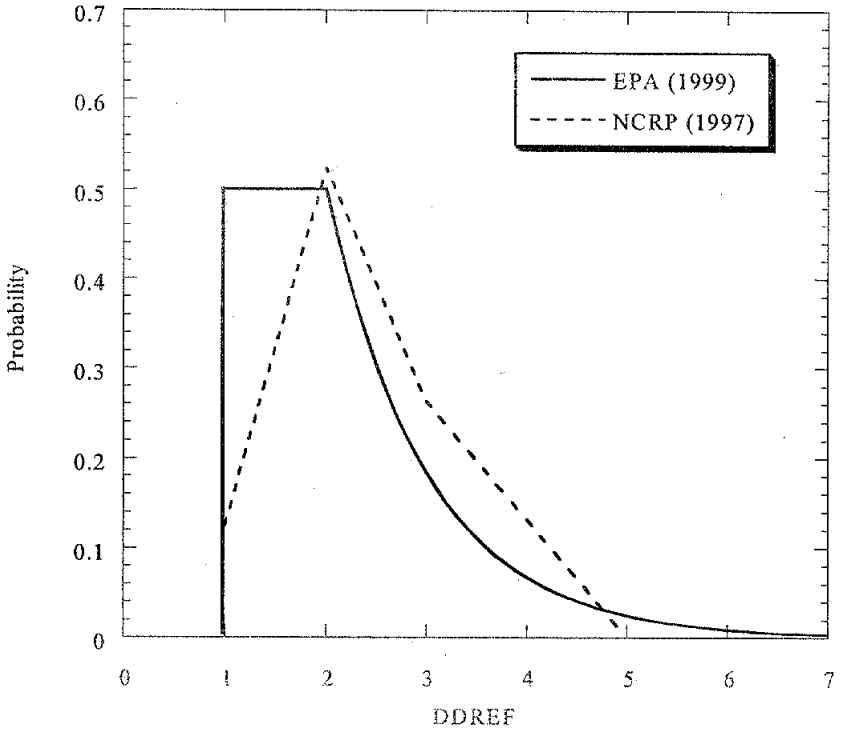

Figure IV.F.1. Probability distribution functions used by different authors to describe the uncertainty in the DDREF.

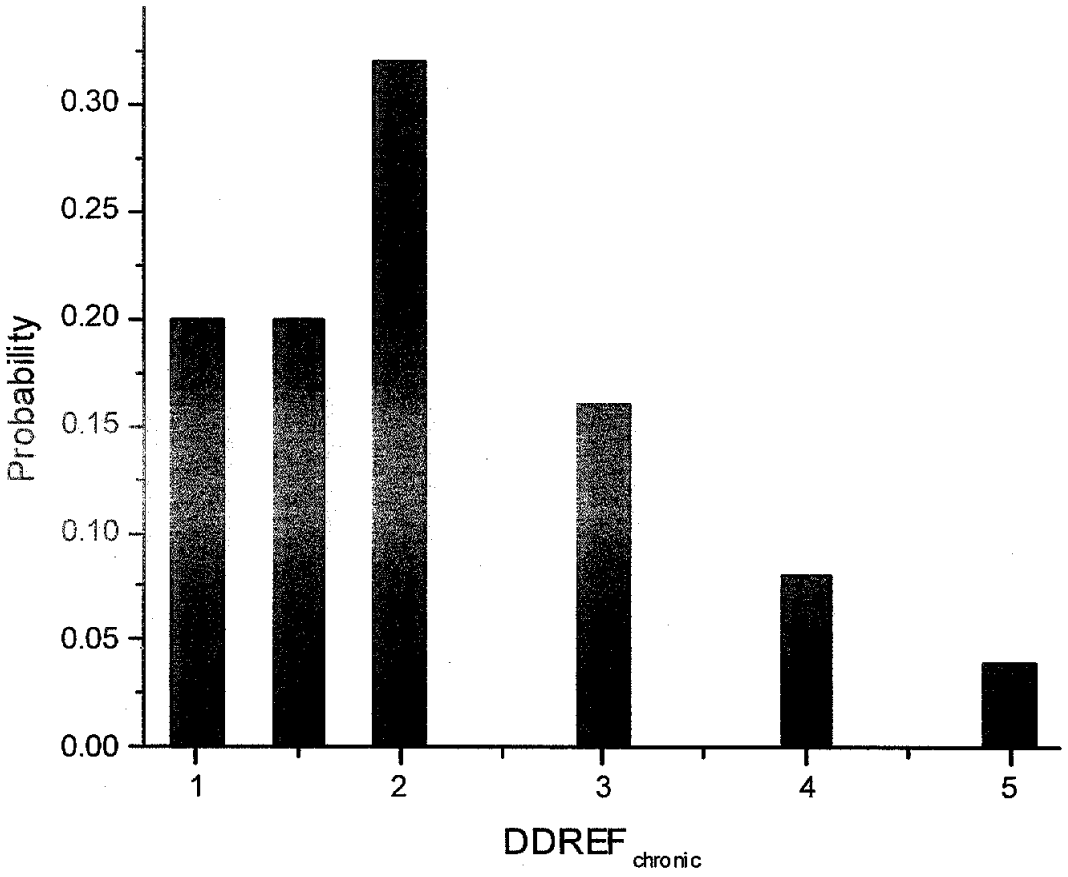

Figure IV.F.2 Illustrative probability distribution function for the dose and dose-rate effectiveness factor applied to chronic exposures. For cancers of the thyroid gland and female breast, the probability distribution is shifted to the left (see text).

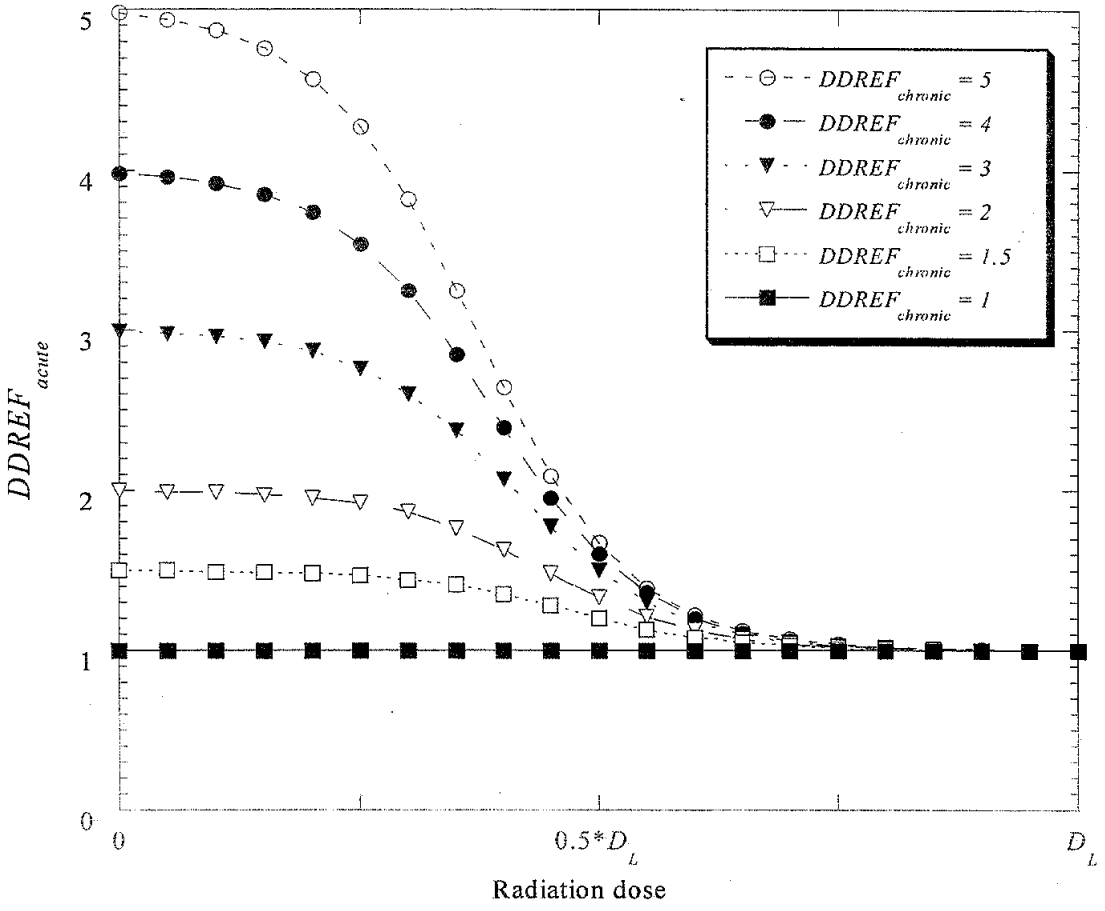

Figure IV.F.3. Variation of $DDREF_{acute}$ as a function of radiation dose for selected values of $DDREF_{chronic}$ for a fixed value of D_L. the lowest dose at which linearity of dose response is assumed to apply.

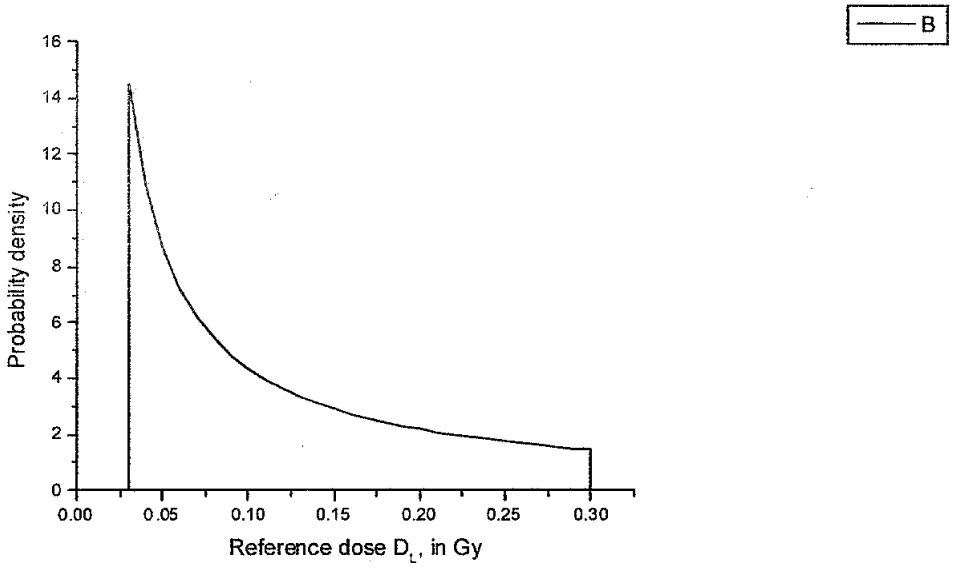

Figure IV.F.4. Log-uniform uncertainty distribution of reference dose D_L, below which the DDREF applies.

G. Relative biological effectiveness (RBE) factors for high-LET radiation

In this report, it is assumed that dose equivalent or weighted dose, in Sv, used as input for calculation of AS was obtained from organ dose, in Gy, using a weighting factor appropriate to the type of radiation and the cancer site involved. The weighting factors account for the relative difference in effectiveness in inducing stochastic effects between different types of radiation and 50-250 kVp x-rays. Such weighting factors have been referred by different names (e.g., "relative biological effectiveness" or RBE, quality factor or Q), depending on their derivation and intended use. For present purposes, "RBE" will suffice.

It is well recognized that there is substantial uncertainty associated with RBE values. Accordingly, an appropriate multiplicative uncertainty factor, denoted f_{RBE}, is introduced here into the calculation of the ERR and its transformation, the AS. This factor is represented as a probability distribution function, and it is specific for a given type of radiation and, for alpha particles, may vary by type of cancer.

For <u>neutrons</u>, it is assumed that the dose provided by the user is based on an RBE value of 10, which is a reasonable value for exposure to neutrons of mixed energies. The RBE for neutrons varies as a function of energy, ranging from 5 to 20 (ICRP, 1991). For tumor induction by low doses from fission neutrons, extreme values up to 200 were reported by Sinclair (1985) and ICRU (1986). Later revisions of the same data gave values up to 60 (NCRP, 1990). In that report, f_{RBE} for neutrons was distributed as lognormal with a geometric mean (GM) of 1 and a geometric standard deviation (GSD) of 1.75. The factor increases the uncertainty of the dose equivalent prescribed by the user without changing its central value. The upper and lower 95% limits for this probability distribution are a factor of 3 above or below the geometric mean. The same distribution was used for all cancer types.

For <u>alpha</u> radiation, it is assumed that the dose provided by the user is based on an RBE value of 20. Specific factors f_{RBE} were derived for lung, liver, and bone cancers, and for leukemia, as indicated in the dose reconstruction study for individuals exposed to ^{239}Pu released from Rocky Flats (Grogan, 1999). A common adjustment factor was assigned for all other cancers.

ICRP Publication 31 (ICRP, 1980) contains the most comprehensive review of the animal studies (mice, rats, and dogs) relating *lung* cancer induction by alpha radiation to that by beta and gamma emitters. This review indicates that the alpha particle RBE for lung cancer is about 30 with a range from 10 to 100. Here, f_{RBE} was defined as lognormal with GM = 1.5 and GSD = 1.8. The upper and lower 95% confidence limits for this probability distribution are a factor of 3.2 above or below the geometric mean.

NCRP Report No. 104 (1990) summarizes the RBE for various alpha emitters as determined from animal studies. For inducing ***bone* cancer**, ^{226}Ra is about 20 times more effective than ^{90}Sr, while ^{239}Pu is 15-17 times more effective than ^{226}Ra. Lloyd et al. (1994, 1995) also estimated a ratio of 16 by comparing cancer induction by monomeric plutonium and ^{226}Ra. By combining these relative values, an RBE of about 320 (20*16) is obtained for ^{239}Pu. These studies generally refer to exposures to very low doses. Thus, such a large RBE may represent an upper bound of the possible values for RBE (i.e., RBE_M as defined by ICRP, 1991). Grogan et al. (1999) concluded that the RBE for bone tumor induction could range from 15 to 320 with a central value of about 50, and that values of RBE larger than 400 are probably unrealistic. Using ^{239}Pu as a surrogate for bone-surface-seeking alpha emitters generally, and the central value of 50, a GSD of 2.4 can be determined so that the upper 99% credibility limit does not exceed 400. The uncertainty factor f_{RBE} was, therefore, defined as lognormal with GM = 2.5 (=50/20) and GSD = 2.4.

For ***leukemias***, an RBE for alpha particles can be derived from the studies of the effects of Thorotrast in humans. Grogan et al. (1999) reviewed the relevant studies and estimated that the RBE values for leukemia range from 1 to 10, with a central value of 3. In this case, the f_{RBE} was defined as lognormal with GM = 0.15 (3/20) and a GSD = 2. The upper and lower bounds of the 95% confidence interval for this probability distribution are a factor of 3.8 above or below the geometric mean.

The Thorotrast studies in humans as reviewed by UNSCEAR (1994) are used for *liver* cancer. These studies indicate a range of RBE values from 8 to about 50. Assuming a central value for RBE of 20, f_{RBE} was defined as lognormal with GM = 1 and GSD = 1.75. The upper and the lower bound of the 95% confidence interval for this probability distribution are a factor of 3 above or below the geometric mean.

The RBE for alpha radiation and ***cancers other than liver, bone, lung and leukemia*** was taken to be the same as for neutrons (i.e., a range of 5 to 60, with a central value of 20; NCRP, 1990; Grogan et al., 1999). The factor f_{RBE} was defined as lognormal with GM = 1 and GSD = 1.75. The upper and lower bounds of the 95% confidence interval for this probability distribution are a factor of 3 above or below the geometric mean.

Protons are charged particles lighter than alpha particles or other heavy ions. Little is known about the effectiveness of these particles in inducing cancer tumors. The dose equivalent provided by the user is assumed here to be based on an RBE value of 5, as recommended by ICRP (1991). In that report, the uncertainty in the RBE for protons was considered the same as the uncertainty in the RBE for alpha particles. That is, the RBE factor f_{RBE} for protons has GM =1, but GM =1.8 for lung cancer, 2.4 for bone cancer, 2 for leukemias, and 1.75 for liver and for all

other cancers.

For all types of **low-LET radiation** (gamma, x-rays, and electrons), the RBE was assumed to be 1. That is, all low-LET radiation are assumed to have the same effectiveness in inducing cancer as 50-250 kVp x-rays. This assumption does not take into consideration that low doses of 50-250 kVp x-rays are actually 2-3 times more effective than high-energy gamma rays (Sinclair, 1985). No adjustments related to the uncertainty in the RBE were included for low-LET radiation.

H. Transfer of ERR from the Japanese to the U.S. population

A major concern in using data from Japanese A-bomb survivors to estimate risks for specific cancers in a U.S. population is that baseline risks differ between the two populations and the dependence of radiation risks on baseline risks is not known with certainty. For example, baseline cancer rates for breast, lung and colon cancer are smaller in Japan than in the United States, while rates for stomach and liver cancer are much higher in Japan. Estimation of risk for a U.S. population based on the dose response coefficients derived from A-bomb survivor data is commonly referred to as the "transfer" or "transportation" problem. A more detailed discussion of the transfer problem appears in NCRP Report 126 (NCRP, 1997).

Two simple solutions are the so-called "multiplicative" and "additive" transfer models, in which estimates of excess relative risk (the ratio between excess and baseline risk) and absolute risk (the difference between the estimated cancer rates with and without exposure), respectively, are applied to the second population (in this case, the U.S. population). The multiplicative transfer model is biologically plausible to the extent that ionizing radiation exposure can be assumed to act as an "initiator" of a process whose likelihood of resulting in cancer depends upon the action of "promoting" agents, if these "promoting" agents are responsible for the difference in baseline rates between the two populations, or, alternatively, if radiation were to act as a promoter of the carcinogenic effects of other agents that are differentially effective in the two populations. In this view, the excess risk from radiation exposure would be greater in a normally high-risk population than in a normally low-risk population. The additive transfer model is plausible to the extent that radiation can be assumed to act mainly as an initiator and the difference between population baseline rates can be assumed to be due to the differential effects in the two populations of other "initiator" carcinogens that act similarly to radiation. In this view, the additional cancer risk burden of radiation exposure would be independent of the population baseline rate.

Several approaches have been used for transferring risk estimates based on the Japanese A-bomb survivor data to other populations. The multiplicative transfer model was used by UNSCEAR (1988) for the world population and in the BEIR V report (NAS, 1990) for the U.S. population.

The additive transfer model was used in the BEIR III report (NAS, 1980) and the 1985 NIH report (NIH, 1985). The two transfer models can lead to very different estimates of radiation-related risk for certain cancers for which baseline risks differ greatly between Japan and the U.S. (Land, 1990). Each model receives some support from site-specific comparisons, but there are few sites for which meaningful analytic comparisons can be made. If population differences in cancer rates may be due to both initiating and promoting agents, it is likely that both additive and multiplicative model interactions with radiation may take place, and that some kind of mixture model may be appropriate. For example, the ICRP (1991) used the arithmetic mean of the ERR values obtained by the two transfer models for all solid cancer types combined (Land and Sinclair, 1991), and the Environmental Protection Agency (Puskin and Nelson, 1995) used the geometric mean (except for liver cancer associated with exposure to the radioactive contrast medium thorotrast, for which a multiplicative transfer model was preferred, and bone cancer from exposure to injected ^{224}Ra, for which an additive transfer model was chosen). More recent reports have used uncertain (i.e., randomized) linear or geometric combinations, weighted in various ways, of the additive and multiplicative transfer models for the estimation of total risk of cancer mortality (EPA, 1999).

Mortality rates for all types of cancer combined vary relatively little by nation, compared to site-specific variation. The initial ERR_{1Sv} value for mortality from all cancers combined used in NCRP Report 126 (NCRP, 1997) was the rounded average of multiplicative and additive transfer model estimates from the LSS mortality data for five different national populations (ICRP, 1991, Land and Sinclair, 1991). Thus, the problem for that report was not how to estimate ERR_{1Sv} for a US population, but to determine the uncertainty associated with estimating ERR_{1Sv} in a particular way. Their solution was an uncertainty factor F(T), distributed as LN(1, 1.3).

For the present report, the problem is how to estimate site-specific and age-specific values of ERR_{1Sv} for the US population in the presence of possibly large differences in baseline rates and the absence of useful information about which model might be correct. Our approach is to use a random linear combination between the additive and multiplicative models,

$$(ERR_{1Sv})_{US} = y \times (ERR_{1Sv})_{mult} + (1-y) \times (ERR_{1Sv})_{add},$$

where the random variable y varies between -0.1 and 1.1. Here, $(ERR_{1\,Sv})_{mult}$ is the site-, sex-, and age-specific excess relative risk at 1 Sv obtained from statistical analysis of the Japanese A-Bomb survivor data and adjusted for random and systematic errors in dose to individual A-bomb survivors (see IV.D above). $(ERR_{1\,Sv})_{add}$ is the same value, adjusted for the corresponding ratio

between baseline rates in the two countries:

$$\left(ERR_{1Sv}\right)_{add} = \left(ERR_{1Sv}\right)_{mult} \cdot \left(\frac{B_{Japan}}{B_{US}}\right)$$

Here, B_{Japan} and B_{US} are the sex- and site-specific, age-adjusted background cancer incidence rates in Japan (a surrogate for the A-Bomb survivor cohort) and the US population, respectively, both age-standardized to the world population age distribution (Parkin, 1997). The geometric standard deviation of the ratio, B_{Japan}/B_{US}, was adjusted by the method of DerSimonian and Laird (see IV.D, **thyroid cancer**) for variation in age-standardized rates among the five ethnic subgroups of the US population (African American, Asian and Pacific islander, Hispanic, Native American, and non-Hispanic White).

The coefficient y of the linear combination can be used to favor one model or the other according to the weight of evidence. For instance, y=0 corresponds to the *additive* model, $y = 1$ to the multiplicative model, and $y = ½$ to the arithmetic average of the two. A Monte Carlo simulation is used to express uncertainty about y, with y values sampled according to the following probability density distribution:

$$f(y) = \begin{cases} 9.091 \cdot (y + 0.1) & -0.1 \le y < 0.0 \\ 0.9091 & 0.0 \le y < 1.0 \\ 9.091 \cdot (1.1 - y) & 1.0 \le y \le 1.1 \end{cases}$$

The constant probability density shown above for y values between 0 and 1 reflects a complete lack of knowledge about the appropriateness of particular weighted averages of the additive and multiplicative transfer models, and the assignment of a small probability weight (9%) to values less than zero and larger than one allows for the (subjectively unlikely) possibility that radiation-related cancer risk might be negatively correlated with population baseline risk.

For breast and stomach cancer, more information is available and, thus, the "uninformed" trapezoidal density given above and in Figure V.G.1 may be modified by redistributing some of the weight to the additive transfer model in the case of breast cancer (Land et al, 1980, Little and Boice, 1999, Mattson, 1999) or the multiplicative model for stomach cancer (Griem et al, 1994). Thus, for breast cancer, a probability weight of 50% was assigned to the *additive* transfer model ($y = 0$), and 50% was assigned to the trapezoidal probability density distribution. For stomach cancer, a probability weight of 33% was assigned to the *multiplicative* model ($y = 1$), and 66% to the trapezoidal distribution, while for thyroid cancer the weighting was 50% on the multiplicative

model and 50% on the trapezoidal distribution. The cumulative distribution functions for these distributions are compared with that for the "uninformed" distribution in Figure IV.G.2.

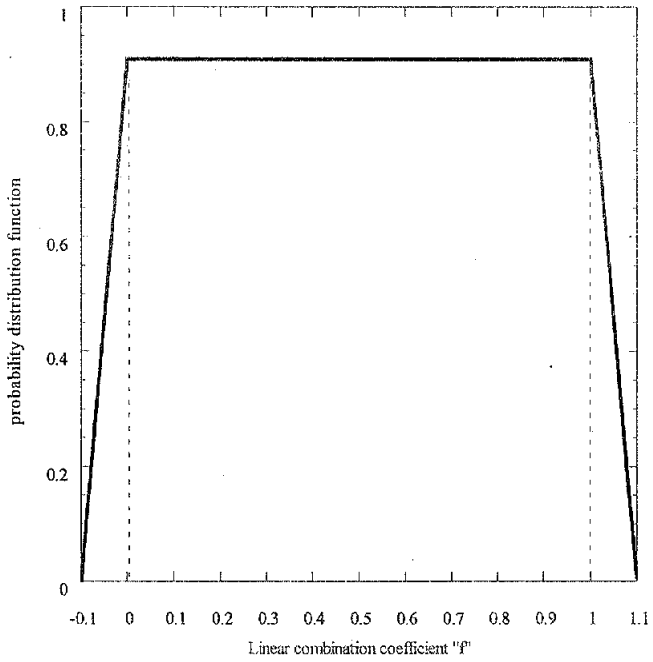

Figure IV.H.1 Probability density function assigned to the coefficient *y* for linear combination of the multiplicative (*y*=0) and additive (*y*=1) models for transfer of excess relative risk from one population to another, for most types of cancer.

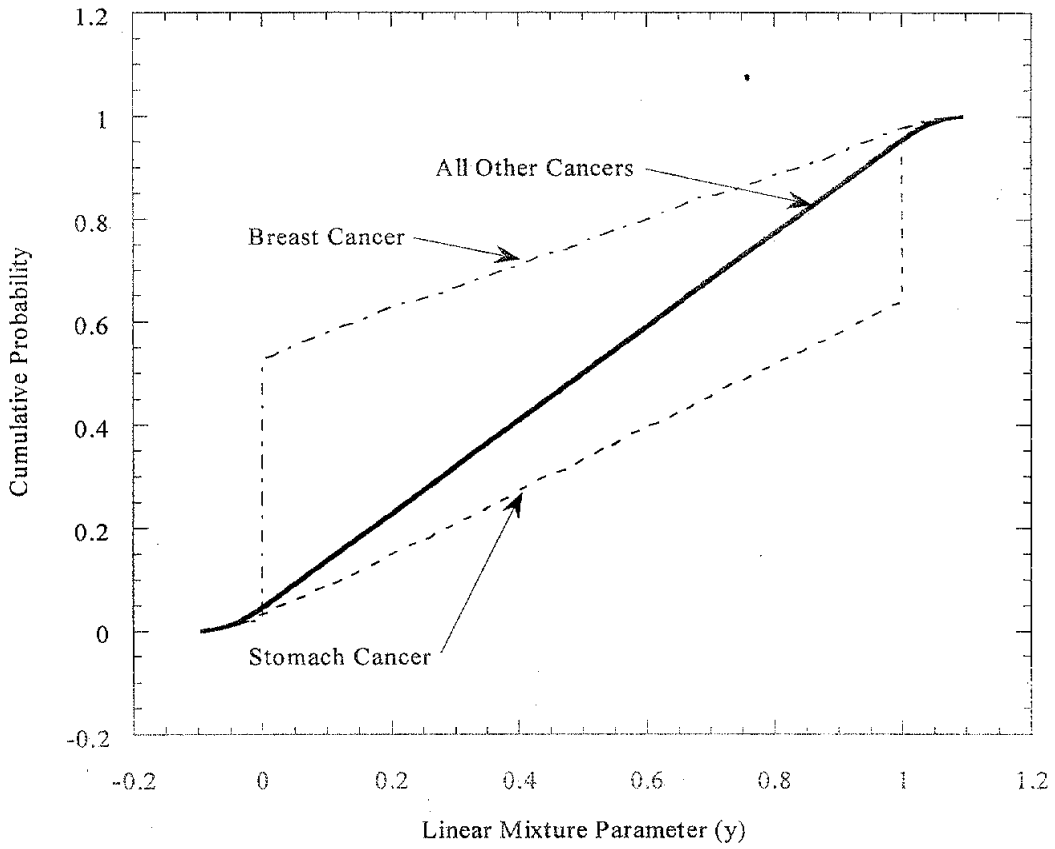

Figure IV.H.2 Cumulative distribution functions for the coefficient y used for computing a weighted average of the additive and multiplicative models for transfer between populations:

transfer model = y × multiplicative model + (1-y) × additive model.

Note that the transfer model for breast cancer places 50% probability on the model in Figure IV.F.1 and 50% on y=0, whereas for stomach cancer 33% is placed on y=1 and the remainder on the model in Figure IV.H.1. The multiplicative transfer model is used for thyroid cancer.

I. Modification by epidemiological risk factors

Site-specific studies of radiation dose and cancer risk, in LSS sample and in other exposed populations continually followed up over time, generally proceed in a series of steps beginning with the evaluation of evidence that a dose-related excess risk actually exists. Usually, the first modifiers of dose response to be considered are gender, age at exposure, age at observation (attained age), and time following exposure, since information about them is usually obtained at the same time as information on radiation exposure and disease occurrence. Modification of dose response by other factors is a more difficult problem, because it usually requires special data-gathering efforts, such as with an embedded case-control study. Informative studies of interaction between radiation dose and epidemiological risk factors have been carried out for reproductive history in the case of breast cancer and for smoking history in the case of lung cancer.

1. General formulation. If radiation dose D and factor *f* are multiplicative in effect, then the excess relative risk associated with exposure D is independent of *f*, i.e., $ERR_{D|f} = ERR_D$.. If D and *f* are additive in effect, then the conditional ERR associated with D given exposure *f* is

$$ERR_{D|f} = ERR_D/(1+ERR_f).$$

2. Breast cancer: interaction of radiation and age at first full-term pregnancy. Reproductive history is known to be an important breast cancer risk factor. In particular, early age at first full-term pregnancy has been shown, in virtually every population that has been studied, to be protective. A case-control interview study of female A-bomb survivors examined the interaction of this risk factor with radiation dose (Land et al, 1994), and found that an additive interaction model was rejected, whereas a multiplicative interaction model was consistent with the data. A general risk model,

$$R_{mix}(D,X;\beta,\theta) = (1 + \alpha_E D)(1 + \beta X/\{1 + \alpha_E D\}^{\theta}),$$

was used to distinguish between the multiplicative model (corresponding to $\theta=0$),

$$R_{mult}(D,X;\beta) = (1 + \alpha_E D)(1 + \beta X),$$

and the additive model (corresponding to $\theta=1$),

$$R_{add}(D,X;\beta) = 1 + \alpha_E D + \beta X.$$

Here, D is radiation dose, X is age at first full-term pregnancy, α_E is a parametric function describing radiation dose response as a function of age at exposure, and β is an unknown parameter corresponding to X. The maximum likelihood estimate of the parameter θ was negative (-0.25) (Land, 1994) and the likelihood distribution placed less than 10% probability on

values greater than zero in calculations performed for the present report. Thus, it appears that very little additional uncertainty would be contributed by allowing for deviations from the multiplicative interaction model, for which no adjustment of ERR_{1Sv} is required for age at first full-term pregnancy. This report therefore makes no uncertainty adjustment for this factor.

3. Lung cancer: interaction of radiation dose with smoking history. Interaction analyses of A-bomb survivors (Blot et al, 1983) and uranium miners (NAS, 1988) failed to discriminate between additive and multiplicative interaction models, although the BEIR IV committee concluded that the data were more consistent with a multiplicative interaction (NAS, 1988). More recently, Lubin and Steindorf (1995) modeled joint relative risks for smoking history (ever vs. never) and exposure to inhaled radon decay products among 6 cohorts of U.S. uranium miners for which such information was available. They concluded that, at that level of smoking history detail, the best-fitting interaction model was intermediate between the additive and multiplicative interaction models. The BEIR VI committee (NAS, 1999) applied the Lubin-Steindorf approach using more recent data, and concluded that both the multiplicative and (especially) the additive interaction models were statistically inconsistent with the data.

In the 1985 NIH report, it was assumed that the interaction of smoking and exposure to low-LET radiation was additive with appropriate assigned shares obtained by multiplying the ERRs by the factors indicated in columns 2 and 3 of Table IV.G.1. These factors were calculated as described on pp. 48-51 of the 1985 report and based on lung cancer relative risks by smoking category given by Rogot and Murray (1980) and the distribution of the U.S. population by smoking status in 1964-65 as published by the National Center for Health Statistics (1967). These factors can be updated by using 1993 information on the smoking status distribution provided by the Centers for Disease Control (1995). This distribution differs substantially from that used in the 1985 report as shown in Table IV.G.2. Because the CDC report did not provide data on amount smoked, it was assumed that among current smokers the distribution by amount smoked was the same as that used in the 1985 report (p.50). It was also assumed that the relative risks by smoking category remained appropriate. The revised factors for additive transportation are given in the last two columns of Table IV.G.1.

Table IV.I.1. Factors for adjusting the lung cancer ERR_{ISv} for smoking status under the assumption of an additive interaction model.

	Used in the 1985 report		Used in deriving uncertainty distribution for this report (W_S*)	
Smoking category (S)	Males	Females	Males	Females
Total	1.00	1.00	1.00	1.00
Never smokers	6.81	4.64	4.74	3.90
Former smokers	1.71	1.17	1.19	0.98
Present smokers (all)	0.604	0.411	0.42	0.35
<10 cigarettes/day	1.75	1.19	1.22	1.00
10-20 cigarettes/day	0.71	0.48	0.49	0.41
21-39 cigarettes/day	0.41	0.28	0.28	0.23
40+ cigarettes/day	0.29	0.20	0.20	0.16
Ever smoker (Present and former smokers)	0.73	0.47	0.51	0.41

Table IV.I.2. Percentage of the U.S. Population in Various Smoking Categories

	Used in the 1985 report (Status in 1964-65)		Used in this report (Status in 1993)	
Smoking category (S)	Males	Females	Males	Females
Never smokers	29.8	59.0	42.4	57.8
Former smokers	19.2	7.8	29.9	19.7
Current smokers (all)	51.0	33.2	27.7	22.5
<10 cigarettes/day	13.6	13.5	7.4*	9.2*
10-20 cigarettes/day	24.7	15.0	13.4*	10.2*
21-39 cigarettes/day	11.2	4.4	6.1*	3.0*
40+ cigarettes/day	1.4	0.3	0.8*	0.2*

*These percentages were obtained by assuming distribution by amount smoked among current smokers was the same as that used in the 1985 report (p.50)

For the purposes of this report, the ERR_{1Sv} for lung cancer is multiplied by a factor W_S taken to be $x + (1 - x)W_S^*$, where S indexes smoking categories, the W_S^* are the factors given in columns 3 and 4 of Table IV.G.1, and x is assumed to follow a triangular distribution (0, 1, 1.1). This uncertainty distribution allows the ERR_{1Sv} for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$), with a probability of about .10 for a super-multiplicative interaction ($x > 1$). The median of this distribution is .74, and at this value, $W_S = 1.97$ for male never-smokers, $W_S = 0.87$ for male ever-smokers, $W_S = 1.75$ for female never-smokers, and $W_S = 0.85$ for female ever-smokers. Thus, at the median value, the ERR_{1Sv} for never smokers is a little more than twice that for ever-smokers. A ratio of two was used by the BEIR VI committee, and was obtained from analyses of uranium miner data (NAS, 1999, pg. 154).

J. Susceptible subgroups. Genetic susceptibility to radiation carcinogenesis is known to occur in patients with xeroderma pigmentosum or hereditary retinoblastoma, and the possibility of other such associations is of great interest for theories of carcinogenesis. However, most known genetic syndromes predisposing to cancer are rare, and interactions with radiation dose have not been quantified (ICRP, 1999). Such interactions therefore have not been explored in the present report.

K. Additional sources of uncertainty

As mentioned above (section IV.A), AS is not intended to represent the probability that a particular individual's cancer was caused by his or her radiation exposure, but rather, the fraction of cases of a particular kind of cancer, diagnosed at a particular age among a large group of U.S. residents with a similar exposure history, that would not have occurred in the absence of that exposure. Possible modifying effects of age at exposure, gender, age at diagnosis, and time following exposure, plus (for certain sites) smoking history and reproductive history have been studied and that information has been incorporated into the model. The working group has also introduced crude uncertainty factors for transfer of risk coefficients between populations with different baseline risks.

It is likely that there are other sources of bias and uncertainty influencing radiation-related risk and AS, about which we have no useful information and, thus, no solid grounds for taking action. However, a precedent was established in the original radioepidemiological tables report (NIH, 1985), and in NCRP Report 126 (NCRP, 1997) for use of a catch-all factor for additional, non-specific sources of uncertainty. We have followed that precedent by introducing a residual "scale factor," lognormally distributed with GM = 1 and GSD = 1.5.

V. Features of the Approach

A. This is an interim update.

As noted in III A and B, in the last 15 years additional epidemiologic data have become available, and these data have considerable potential for modifying and refining the AS tables now in use. Also, several efforts have been made to summarize data that were not available at the time the NIH report was published, and to develop risk estimates based on these data. However, these efforts have not evaluated data from studies published in very recent years, including particularly the latest updates of the Japanese A-bomb survivor incidence and mortality data. For example, the most recent BEIR assessment was published in 1990 and the most recent ICRP assessment was published in 1991. Thus, much of the available new data has not yet been evaluated by expert committees charged with developing and recommending risk estimates. In addition, new data, including updated follow-up for cancer incidence in the A-bomb survivors, are expected to become available soon.

In part because of this situation, the BEIR VII - Phase 1 Committee has recommended that a reassessment of the health effects of exposure to low levels of ionizing radiation be conducted, and the BEIR VII - Phase 2 has been formed to undertake this task. It is anticipated that the present report will be revised after the BEIR VII committee recommendations become available, expected in two or three years. Thus, the AS algorithms described here must be regarded as an interim update rather than one based on risk models endorsed by an official national or international committee; therefore, it might differ appreciably from future tables based on the BEIR VII - Phase 2 report. The current update nevertheless provides AS values that are based on more up-to-date data and models than previously, and also makes notable improvements in the treatment of uncertainties.

B. Similarities to the 1985 report

Because this update must be regarded as interim, the time frame and scope for carrying out data analyses and model development were limited. For this reason, we did not begin from scratch to develop new models, but instead used the models used for the 1985 AS tables as a starting point, amending them as needed to reflect the most important changes in risk coefficients and risk modeling approaches. Specifically, the following features of the 1985 tables were retained:

1. Assigned share estimates based primarily on A-bomb survivor data. The AS values in the 1985 report were based primarily on the A-bomb survivor data, although in some cases other data were also used. The AS values in the current report are based almost entirely on A-bomb survivor data and, with the exception of thyroid cancer, did not directly make use of data from studies of

persons exposed for medical reasons, or from studies of workers and others exposed at low doses and dose rates. Estimates based on data from low dose studies would be far too imprecise to meet the needs of the AS tables, where estimates for specific cancer, ages at exposure and gender are required. It is noted, however, that considerable uncertainty has been allowed for extrapolation from high doses and dose rates.

2. Cancer sites evaluated include most of those in the 1985 report. Our choice of cancer sites includes all of those in the previous report, except for bone cancer associated with injection of ^{224}Ra and lung cancer associated with inhalation of radon decay products. Some new cancer categories have been added.

3. Site-specific assigned share estimates based on data for that site alone. The AS values for each cancer site were based on analyses of A-bomb survivor data for that site only, as in the 1985 report. Estimates of both the overall risk coefficients and parameters expressing the dependence on age at exposure and gender were based only on data for the site being evaluated. Consideration was given to conducting joint analyses of several cancer types (see Pierce and Preston, 1993), testing whether various parameters were comparable among cancer types, and then using common estimates of selected parameters in developing site-specific AS values. This approach has the potential advantage of greater statistical precision in the estimated AS values, but the disadvantage of difficult-to-quantify uncertainty in whether the chosen models are appropriate. Although we think the approach is worthy of consideration for future risk assessments and AS estimation, we judged it too great a departure from the previous approach to use at this time.

4. Time since exposure was handled in the same manner. For all cancer types except leukemia and bone cancer, the 1985 models were based on the assumption that, after a minimal latent period, the excess relative risk per Sv (ERR/Sv) remained constant over time since exposure and therefore did not depend additionally upon attained age. We have also made these assumptions unless there was evidence to the contrary based on the data analyzed. In fact, modification by time since exposure is included only in the models for leukemia, and modification by attained age is included only in the models for colon cancer and kidney cancer.

C. Important changes

1. Estimates were obtained for all cancer sites for which the calculations could be performed, not just those established as "radiation-related." A working assumption was that radiation exposure might be a causal factor for any site or type of cancer, at some exposure level and under some conditions. This assumption obviates the question of whether or not a particular kind of cancer could be caused by radiation; rather, the most pertinent problem is what values of

AS are consistent with current scientific information in a particular instance of cancer following a particular exposure. The working group therefore has provided for the calculation of uncertainty distributions for AS, for all cancer types for which there were relevant data available from the sources on which the present report is based.

2. Assigned share estimates were based on incidence instead of mortality data. Although the 1985 NIH report used incidence data from site-specific studies of leukemia and cancers of the thyroid gland, female breast, and salivary gland, it relied mainly on data from the LSS mortality survey. By contrast, the present report bases its estimates and models on data from the LSS Tumor Registry and, in the case of thyroid cancer, from a pooled analysis of data from several studies. The RERF Tumor Registry is now a highly reliable source of cancer incidence information with good coverage of that part (80%) of the surviving LSS sample resident in the environs of Hiroshima and Nagasaki (Mabuchi, 1994); this coverage goes far toward matching the main advantage of the LSS death certificate data, viz., completeness of ascertainment for a general population of both genders and all ages, acutely and simultaneously exposed to a range of whole-body radiation doses and followed uniformly over time. Follow-up for the mortality series and for incident diseases covered by the Leukemia Registry began on October 1, 1950, the entry date for members of the LSS cohort; for the LSS Tumor Registry, follow-up began on January 1, 1958. The later beginning of the tumor registry is a serious problem only for cancers of short latency, most of which are covered by the Leukemia Registry or by site-specific studies that involved special case-ascertainment efforts for the period 1950-1957, and for estimation of excess risk among persons who were over 50 or 60 years of age when exposed. Comprehensive statistical analyses of site-specific cancer incidence through 1987 were presented for solid cancers and leukemia (Thompson, 1994, Preston, 1994) and, especially important for present purposes, the original data sets were made available by RERF on disk.

3. Assigned share estimates are based on analyses conducted for this specific purpose instead of published risk estimates. For the 1985 report, assigned shares were estimated from tabulated published estimates, primarily from the BEIR III report. The availability of grouped numerator and denominator data from LSS Tumor Registry for 1958-1987, plus similar data for site-specific incidence studies of salivary gland and female breast cancer, and for a pooled study of thyroid cancer in several irradiated populations, allowed the present working group to model site-specific risks directly. This permitted the working group to determine independently the dependence of dose-specific excess relative risk on important modifying factors, and to choose models of suitable complexity.

4. Modeling of the excess relative risk (ERR) instead of the excess absolute risk (EAR). The ERR was modeled directly rather than converted from tabulated estimates of EAR, as was done in

the 1985 report. Note that assigned share (AS) is a simple, monotonic function of the ERR, AS = ERR /(1+ERR).

5. Radiation dose response and adjustment for low dose-rate exposure Because estimates obtained directly from epidemiological data on populations exposed only at low doses are very imprecise, it is necessary to extrapolate from risks that have been estimated from persons exposed at higher doses (and dose rates) than those of direct interest. The estimates used in this report are based on Japanese atomic bomb survivor data, and estimates based on these data tend to be driven by the cancer experience of persons exposed to doses that exceed 1 Gy. This is much larger than doses for which AS values are usually desired, which are almost always less than 0.1 Gy and often much smaller.

Although most epidemiological data for solid cancers are compatible with a linear dose-response function in which risk is proportional to dose, curvilinear forms cannot be excluded. On the other hand, dose-response analyses of leukemia risk have consistently shown evidence of upward curvature consistent with a quadratic function of dose having a substantial linear component ("linear-quadratic" or "L-Q" for short).

a. Method used in the 1985 NIH report The 1980 BEIR III committee chose as their "preferred" dose response model an L-Q model in which risk was proportional to $D + D^2/1.16$, where D is organ-specific dose in Gy, and the 1985 NIH tables committee adopted that form for their report. Thus, with two exceptions (breast and thyroid cancer, for which linearity was assumed), the estimated excess risk per unit dose was a little more than half as high at 0.1 Gy as at 1 Gy. Another consequence was that the risk per unit dose of the sum of several exposures, each less than 0.1 Gy and separated in time, or a chronic exposure (treated much the same as the sum of many very small exposures) was estimated to be about half as high as that for a single, acute exposure of about 1.2 Gy.

b. Method used in the present report The approach used for the present report was to treat leukemia risk as proportional to $D + D^2$, since estimates of the D^2 coefficient are generally inexact but in the neighborhood of unity and significantly greater than zero. For all other cancers, the risk was assumed to be linear (proportional to D) for curve-fitting purposes but with a dose-and-dose-rate-effectiveness factor (DDREF) applied to reduce estimated risk at low doses and dose rates. The DDREF approach was chosen because it is consistent with recommendations by the International Commission on Radiation Protection (ICRP 60) and because instances of a linear dose response have been observed above a certain level in combination with a DDREF of 2 or more at lower levels, in experimental studies of radiation carcinogenesis using fractionated exposures (R. Ullrich, personal communication).

6. Method for modeling the modifying effects of gender, age at exposure, time after exposure, and age at observation. The model for the 1985 report was based on separate EAR coefficients for each of five age-at-exposure categories, and for the two genders; this was done for all specific cancers other than leukemia although in some cases the younger ages at exposure were omitted. The approach in the present report was to model the ERR as a function of gender (g), age at exposure (e), age at observation (a), and time after exposure (t), treating all but gender as continuous variables, e.g.,

$$ERR(D,g,e,a,t) = \alpha D \exp(\beta g + \gamma e + \delta a + \epsilon t).$$

Modifying factors g, e, a, and t were included in the model only if the improvement in fit was statistically significant. This allowed us to select the most parsimonious models (in terms of the number of parameters), and provided the basis for evaluating statistical uncertainty in age- and gender-specific estimates. With the exception of leukemia and cancers of the colon and kidney, it was unnecessary to include modifying variables other than gender and age at exposure.

7. Transfer of estimates between populations. An important source of uncertainty is the applicability of risk estimates derived from Japanese A-bomb survivor data to a contemporary U.S. population, especially for cancer types where baseline risks for the two countries differ markedly. On the basis of comparisons of leukemia and breast cancer risk in different populations (BEIR III, Land et al, 1980), transfer between populations in the 1985 NIH report was based on the assumption that absolute risks were comparable, and no attempt was made to evaluate the uncertainty resulting from this choice. For most cancer sites, however, there are few quantitative data other than those available from the LSS, and it cannot be excluded that other transfer models may be appropriate for different cancer sites (Land 1990, Land and Sinclair 1993, NCRP-126, EPA 1999). Moreover, the choice of transfer model involves considerable uncertainty. In the current report, uncertainty from this source has been evaluated, with central estimates chosen to fall in between the NIH model and a model in which relative rather than absolute risks are assumed comparable for Japanese and US populations. Cancers of the thyroid were treated somewhat differently, as discussed in IV.G above.

8. Treatment of uncertainty. The treatment of uncertainty is similar to that in the 1985 report in that uncertainties from each of several components or sources are evaluated separately and then combined into an overall assessment based on the assumption that uncertainties from different sources are independent. It is also similar in that many sources could not be evaluated using rigorous statistical procedures, but required subjective judgements of the investigators. However, the treatment of uncertainties in the updated report differs from the 1985 report in several respects. First, components of uncertainty that were not evaluated earlier have been added,

including especially statistical variability in the risk coefficients and uncertainty resulting from transferring risk coefficients based on Japanese A-bomb survivors to a contemporary U.S. population. Second, uncertainty distributions were selected to reflect available data and the best judgment of the investigators, and were not limited to log-normal distributions as was the case in 1985. Third, Monte Carlo simulations were used to combine uncertainties, a feature that made flexible selection of uncertainty distributions possible. Fourth, uncertainty was not treated as an "add-on", developed after the central estimates had been determined, but rather was a fundamental part of the process. That is, emphasis was not on determining single point estimates, but on developing overall uncertainty distributions, calculated by combining the uncertainty distributions from each of the contributing sources. Given an uncertainty distribution, it is of course possible to determine medians, means, and various percentiles or credibility limits. Finally, the on-line computer software (IREP) incorporates "customized" Monte Carlo simulations to obtain the distribution of a desired AS, taking into account the exposure scenario, certain characteristics of the individual, and the specific type of cancer.

The above modifications drew heavily on developments in uncertainty analysis that have occurred since 1985. The BEIR V report used Monte Carlo simulations to evaluate statistical uncertainty in lifetime risks, but relied on lognormal propagation of errors for evaluating several other uncertainty sources. More recently, both NCRP and EPA have used Monte Carlo simulations, including flexible choice of distributions to describe uncertainties from individual sources. However, NCRP and EPA were primarily concerned with uncertainties in lifetime risks to populations rather than uncertainties in risks for individuals with specific characteristics. Furthermore, NCRP provided a distribution only for the lifetime risk of all fatal cancers, although the report contains discussion of specific cancer types. To our knowledge, the work reported here is the first to evaluate uncertainty distributions for specific AS values associated with any of a wide range of specific cancer types, individual characteristics, and exposure scenarios.

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APPENDIX A: Text of Congressional Mandate and Excerpt from Presidential Statement

Public Law 97-414 - January 4, 1983

"7(b)(1) Within one year after the date of enactment of this Act, the Secretary of Health and Human Services shall devise and publish radio-epidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses. These tables shall show a probability of causation of developing each radiation related cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to the onset of the cancer in question, and such other categories as the Secretary, after consulting with appropriate scientific experts, determines to be relevant. Each probability of causation shall be calculated and displayed as a single percentage figure.

(2) At the time the Secretary of Health and Human Services publishes the tables pursuant to paragraph (1), such Secretary shall also publish--

> (A) for the tables of each radiation related cancer, an evaluation which will assess the credibility, validity, and degree of certainty associated with such tables; and
>
> (B) a compilation of the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation related cancer and has received any given dose.

(3) The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever he deems it necessary to insure that they continue to represent the best available scientific data and expertise."

Excerpt from President Reagan's statement on the occasion of his signing the Orphan Drug Act.

> ". . . there is as yet no consensus among radiation experts in relating human cancers and exposure to low levels of radiation. Yet, Section 7 mandates that probability of causation tables be calculated for even very small dose levels. Accordingly, I am directing the Secretary of Health and Human Services to complete the tables to the extent that may be possible and scientifically responsible, in light of the analysis also mandated by Section 7, which requires him to 'assess the credibility, validity, and degree of uncertainty associated with such tables.'"

APPENDIX B: DHHS Charter - Ad Hoc Working Group to Develop Radioepidemiological Tables

"Purpose

Section 7(b) of Public Law 97-414 directs the Secretary of Health and Human Services to devise and publish radioepidemiological tables that estimate the likelihood that persons with any radiation-related cancer who received specific radiation doses before the onset of the cancer developed the disease as a result of such exposure. The tables must show the probability of causation for each cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to disease onset, and such other categories as the Secretary, after consultation with appropriate scientific experts, determines to be relevant. In carrying out this mandate, the Secretary deems it necessary to establish an Ad Hoc Working Group to Develop Radioepidemiological Tables comprised of scientific experts whose qualifications will insure a thorough, competent and timely completion of the task.

"Authority

42 U.S. Code 217a, Section 222 of the Public Health Service Act, as amended.

This Ad Hoc Working Group to Develop Radioepidemiological Tables is governed by the provisions of Public Law 902-463, which sets forth standards for the formation and use of advisory committees.

"Function

In addition to developing radioepidemiological tables, the Ad Hoc Working Group shall:

1. Assess the credibility, validity, and degree of certainty associated with such tables; and

2. Compile the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation-related cancer and has received any given dose.

The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever necessary, to insure that they continue to represent the best available scientific data and expertise.

"Structure

The Ad Hoc Working Group to Develop Radioepidemiological Tables shall consist of eight

members, including the chairperson. Members and chair- person shall be selected by the Secretary, or designee, from outstanding authorities in the fields of endocrinology, radiation biology and pathology, radioepidemiology, biostatistics, and radiobiology. Members shall be invited to serve for a period of one year. Management and support services shall be provided by the Office of the Director, National Institutes of Health.

"Meetings

Approximately eight meetings shall be held at the call of the chairperson who shall also approve the agenda. A government official shall be present at all meetings. Meetings shall be conducted and records of proceedings kept as required by applicable laws and Department regulations. Meetings shall be open to the public, except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

"Compensation

Members who are not full-time Federal employees shall be paid at the rate of $100 per day, plus per-diem and travel expenses in accordance with Standard Government Travel Regulations.

"Annual Cost Estimate

Estimated annual cost for operating the Ad Hoc Working Group, including compensation and travel expenses for members but excluding staff support, is $36,700. Estimated annual man years of staff support required is one at an estimated annual cost of $49,213.

"Reports

Section 7(b) of Public Law 97-414 directs that within one year after the date of enactment of this Act (January 4, 1983), the Secretary of Health and Human Services shall publish the radioepidemiological tables. The Ad Hoc Working Group will complete its task as outlined in the Function section of this document and submit these findings to the Director, National Institutes of Health, by October 15, 1983.

"Termination Date

Unless renewed by appropriate action prior to its expiration, the Ad Hoc Working Group to Develop Radioepidemiological Tables will terminate on May 15, 1984.

Approved:

8-4-83
Date

(signed) Margaret M.. Heckler"
Secretary

APPENDIX C: Computational Details

Uncertainty due to sampling variation

As described in Section IV, uncertainty due to statistical variation was approximated by likelihood profile distributions. These were based on analyses of A-bomb survivor cancer incidence data, and were obtained for the ERR associated with each type of cancer. For some cancers, separate functions were obtained for the two sexes and for specified ages at exposure and/or times since exposure in 5- or 10-year intervals beginning at 0, or ages at diagnosis in 5- or 10-year intervals beginning at age 20 or 30. Table IV.B.1 shows the cancer types and whether or not the ERR varied by sex, age at exposure, age at diagnosis, and time since exposure.

For use in IREP, the likelihood profile distributions were specified approximately, using likelihood-based confidence bounds in place of distribution percentiles: 0.25%, 0.50%, 1.25%, 2.50%, 5.00%, 12.50%, 15.85%, 50% (approximated by the maximum likelihood estimate), 84.15%, 87.50%, 95.00%, 97.50%, 98.75%, 99.50%, and 99.75%. Intermediate values were calculated by cubic spline interpolation (Press et al., 1996). For all cancer types other than leukemia, 400 interpolated points were used to define the likelihood functions. For leukemia, the $ERR_{1\,Sv}$ depends on both age at exposure and time since exposure (see below). Therefore, only one hundred interpolated points were used, in order to reduce the size of the electronic files.

To obtain the $ERR_{1\,Sv}$ for any age at exposure, age at diagnosis, and/or any time since exposure, linear interpolation in the logarithmic scale was performed between the tabulated $ERR_{1\,Sv}$ values. The $ERR_{1\,Sv}$ for leukemia depends on both the age-at-exposure and time-since-exposure. In this case a bilinear two-dimensional interpolation was performed (Press et al. 1996). From the numerical point of view, the cubic spline interpolation between percentiles was performed first. Then, the log-linear interpolation between ages-at-exposure or times-since-exposure was performed for each derived percentile of the likelihood function.

Phasing in the latency period

The analyses described in Section IV-C were based on a model in which the risk was assumed to be zero for a specified minimal latency period after exposure. To avoid an abrupt jump in the ERR, we used a set of scaling factors to estimate the $ERR_{1\,Sv}$ for the years between the end of the latency period and the age at which maximum risk occurs.

For leukemia (all types), the latency period is considered to end 2 years after exposure, although the Life Span Study data cover only the period 5 years and more after exposure. Accordingly, we phased in the fitted ERR, allowing full expression 5 years after exposure. For 2, 3, and 4 years

after exposure, the $ERR_{1\,Sv}$ is estimated as 0.25, 0.5, and 0.75, respectively, times the fitted value for $ERR_{1\,Sv}$ at 5 years after exposure.

The minimum latency period for thyroid cancer was assumed to be about 5 years, and there was no statistically significant evidence of a trend in ERR_{1Sv} with time following exposure. For a smooth transition, and to allow for uncertainty in the minimum latent period, reduced values of $ERR_{1\,Sv}$ were computed for years 3, 4, 5, 6, and 7 years after exposure by multiplying the fitted, specific to age at exposure, by 0.1, 0.25, 0.5, 0.75, and 0.9, respectively.

For all other cancers, a minimal latency period of about 10 years was assumed, with a smooth transition in $ERR_{1\,Sv}$ from zero at 7 years to full estimated value at 13 years; thus, scaling factors 0.1, 0.25, 0.5, 0.75, and 0.9 are applied to years 8, 9, 10, 11, and 12, respectively.

The dose and dose-rate effectiveness factor (*DDREF*)

As discussed in IV.F, for an *acute* exposure, the value $DDREF_{acute} = 1$ is used for doses larger than a randomly generated reference dose D_L, above which the dose response is assumed to be linear. As the dose approaches zero, $DDREF_{acute}$ approaches the values prescribed for chronic exposure, $DDREF_{chronic}$. The mathematical formulation for the transition from $DDREF_{acute} = 1$ at $D = D_L$ to $DDREF_{acute} = DDREF_{chronic}$ at $D = 0$, as graphed in Figure IV.F.3, is as follows:

$$DDREF_{acute} = \begin{cases} 1 & \text{if } Dose \geq D_L \\ \left\{ \dfrac{1}{1 - \left[\dfrac{\left(1 - \dfrac{1}{DDREF_{chronic}}\right)}{1 + e^{\frac{(Dose - I)}{S}}} \right]} \right\} & \text{if } Dose < D_L \end{cases}$$

The parameters I and S are, respectively, the inflection point ($I = 0.5 * D_L$) and the "shape" parameter ($S = I/\ln(500)$); the smaller the values for S, the steeper the increase of the logistic

function 1 + exp((Dose - I)/S).

A graphical representation of the $DDREF_{acute}$ for fixed D_L and selected values of the $DDREF_{chronic}$ is shown in Section IV (Figure IV.C.2). Note that, as the dose approaches zero, the $DDREF_{acute}$ approaches the prescribed $DDREF_{chronic}$. The value of the "shape" parameter was chosen to obtain the least steep increase of the logistic function that still reproduces the $DDREF_{chronic}$ for a zero dose[1].

[1] This relationship ensures that the DDREF for a dose equal to D_L is larger than 0.99.

APPENDIX D

Example AS calculations and comparisons with the 1985 report

This section presents a number of examples of Assigned Share estimated for various hypothetical cases compared with those included in the 1985 Radioepidemiological Tables report. An important difference between the 1985 report and the present update is the total number of types of cancers considered: there were 14 specific and general cancer types included in the 1985 report; while, currently, risk coefficients and associated uncertainties are available for 33 cancer types.

The cases of leukemia are summarized in Appendix Table 1. The first example in that table is for a female exposed at age 5 to a bone-marrow dose of 5 cGy of low-LET radiation, and diagnosed with an acute leukemia at age 9, four years after exposure. By using the 1985 tables one obtains an Assigned Share of 37%.

The present updated methodology (IREP) distinguishes between acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML).a calculation was performed for each type of disease. The central AS estimates using IREP were 38% for ALL and 8.4% for AML. IREP also gave complete uncertainty distributions, with 95% and 99% quantiles 72% and 85% for ALL and 20% and 27% for AML.

Appendix Table 3, Example 3, concerns a woman who had several exposures to low LET radiation and who was diagnosed with esophagus cancer at age 44. There were two acute exposures of 1 and 2 cSv at age 20, a chronic exposure of 9 cSv at age 21, and three acute exposures to 1.1, 0.6, and 0.7 cSv, respectively, at age 25. The 1985 report gave AS = 6% in this case, whereas IREP gave a central estimate of 11% with 95th and 99th quantiles 38% and 42%, respectively.

Similar example cases are presented in Appendix Tables 1 through 12. The differences between the results produced using the 1985 tables and the current version of the tables are not only due to an updated set of risk coefficients, but also because of the adjustments that are explicitly taken into account in applying the risk coefficients to the U.S. population.

Appendix Table 1 Estimates of the Assigned Share [%] for selected example cases of leukemia.

									IREP (percentile of uncertainty dist.)					
LEUKEMIA[a]	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	5	9	4	5	acute	low LET	37	2.3	2.7	38	72	85	Acute Lymphocytic Leukemia
									2.3	3.2	8.4	20	27	Acute Myeloid Leukemia
Example 2	female	45	53	8	5	acute	low LET	4	0	1	7	21	31	Acute Lymphocytic Leukemia
									6	9	19	40	49	Acute Myeloid Leukemia

[a] The 1985 report treated acute leukemia as a group, with no differentiation between myeloid and lymphocytic leukemias.

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 2 Estimates of the Assigned Share [%] for selected example cases of salivary gland cancer.

									IREP (percentile of uncertainty dist.)					
SALIVARY GLAND	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	5	12	7	3	acute	low LET	4	0.018	0.065	0.40	2.0	3.4	Parotid gland
									0.0	0.013	0.19	0.9	1.7	Non-parotid gland
Example 2	male	18	30	12	5	acute	low LET	—[a]	0.44	1.3	7.7	27	42	Parotid gland
									0.0	0.26	3.8	16	24	Non-parotid gland
Example 3	male	7	20	13	6	acute	low LET	22	1.2	3	12	35	50	Parotid gland
		12	20	8	5	acute	low LET		0.32	0.84	6.1	21	30	Non-parotid gland

[a] In the 1985 report, no salivary gland risk coefficients are available for exposure after age 15. AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 3 Estimates of the Assigned Share [%] for selected example cases of esophagus cancer.

									IREP (percentile of uncertainty dist.)					
ESOPHAGUS	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	male	20	50	30	5	acute	low LET	1	0.0	0.0	0.18	3.8	6.8	
Example 2	male	55	59	4	19	acute	low LET	0	0.0	0.0	0.0	0.0	0.0	during the latency period[a]
Example 3	female	20	44	24	1	acute	low LET	6	1.7	2.8	10	28	40	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

[a] The cancer was diagnosed after a period of time shorter than the latency period of the disease.

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 4 Estimates of the Assigned Share [%] for selected example cases of stomach cancer.

									IREP (percentile of uncertainty dist.)					
STOMACH	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	25	50	25	10	acute	low LET	8	1.8	3.0	13	45	55	
Example 2	female	20	44	24	1	acute	low LET	12	1.4	2.4	13	49	64	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							

35	44	9	0.7	acute	low LET

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 5 Estimates of the Assigned Share [%] for selected example cases of colon cancer.

									IREP (percentile of uncertainty dist.)					
COLON	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	45	48	3	5	acute	low LET	0	0	0	0	0	0	during the latency period[a]
Example 2	male	36	55	19	2	acute	low LET	0.1	0.3	0.5	2.0	6.0	8.6	
Example 3	female	20	44	24	1	acute	low LET	2	3.7	6.6	21	49	60	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

[a] The cancer was diagnosed after a period of time shorter than the latency period of the disease.

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 6 Estimates of the Assigned Share [%] for selected example cases of liver cancer.

									IREP (percentile of uncertainty dist.)					
LIVER	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	male	31	59	28	10	acute	low LET	8	1.7	3.7	17	44	58	
Example 2	female	36	55	19	10	acute	low LET	12	0.0	0.0	3.1	22	30	
Example 3	female	20	44	24	1	acute	low LET	38	0.085	0.30	2.8	15	26	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 7 Estimates of the Assigned Share [%] for selected example cases of pancreas cancer.

									IREP (percentile of uncertainty dist.)					
PANCREAS	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	35	50	15	10	acute	low LET	2	0.0	0.0	1.1	5.8	9.4	
Example 2	male	40	51	11	5	acute	low LET	0.49	0.0	0.0	0.38	2.5	4.7	
Example 3	female	20	44	24	1	acute	low LET	8	0.038	0.11	0.93	4.7	7.8	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							

35	44	9	0.7	acute	low LET

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 8 Estimates of the Assigned Share [%] for selected example cases of lung cancer.

									IREP (percentile of uncertainty dist.)					
LUNG	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	male	20	50	30	5	acute	low LET	4	0.19	0.44	2.3	8.2	14	never smoker
Example 2	female	20	44	24	1	acute	low LET	12	1.8	3.5	11	33	44	never smoker
		20	44	24	2	acute	low LET		1.3	2.1	6.8	19	24	former smoker
		21	44	23	9	chronic	low LET		1.3	2.2	6.9	19	25	current smoker (<10 cig./day)
		35	44	9	1.1	acute	low LET		1.0	1.6	5.7	16	22	current smoker (10-19 cig./day)
		35	44	9	0.6	acute	low LET		0.94	1.4	5.2	16	21	current smoker (20-39 cig./day)
		35	44	9	0.7	acute	low LET		0.78	1.4	5.1	15	21	current smoker (>40 cig./day)

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 9 Estimates of the Assigned Share [%] for selected example cases of breast cancer.

									IREP (percentile of uncertainty dist.)					
BREAST	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	10	35	25	10	acute	low LET	13	1.8	2.8	6.6	18	23	
Example 2	female	20	44	24	1	acute	low LET	7	0.86	1.5	4.5	13	20	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 10 Estimates of the Assigned Share [%] for selected example cases of kidney cancer.

									IREP (percentile of uncertainty dist.)					
KIDNEY[a]	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	35	55	20	10	acute	low LET	2	1.3	2.7	10	26	32	bladder
Example 2	male	55	60	5	5	acute	low LET	0	0	0	0	0	0	during the latency period[b]
Example 3	female	20	44	24	1	acute	low LET	4	0.41	0.77	3.2	11	16	kidney
		20	44	24	2	acute	low LET		1.4	2.2	8.0	21	28	bladder
		21	44	23	9	chronic	low LET		4.3	6.6	24	61	73	all urinary organs
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

[a] The 1985 report used "kidney and bladder" as a group. In the current version, risk coefficients are available for "kidney", "urinary bladder" and "all urinary organs" separately.

[b] The cancer was diagnosed after a period of time shorter than the latency period of the disease.

AAE = age at exposure; AAD = age at diagnosis; TSE = time since exposure

Appendix Table 11 Estimates of the Assigned Share [%] for selected example cases of thyroid cancer.

									IREP (percentile of uncertainty dist.)					
THYROID	Gender	AAE	AAD	TSE	Dose (cSv)	Rad. Rate	Rad. type	1985 tables	1st	5th	50th	95th	99th	NOTES
Example 1	female	10	19	9	5	acute	low LET	22	2.2	4.2	15	40	53	
Example 2	female	10	25	15	5	acute	low LET	28	3.8	6	19	43	57	
		15	25	10	2	acute	low LET							
Example 3	female	20	44	24	1	acute	low LET	31	2.5	4.1	15	38	51	
		20	44	24	2	acute	low LET							
		21	44	23	9	chronic	low LET							
		35	44	9	1.1	acute	low LET							
		35	44	9	0.6	acute	low LET							
		35	44	9	0.7	acute	low LET							

APPENDIX E: Interactive Radio-epidemiological Program (IREP)

Access Instructions

AS calculations can be performed using IREP by accessing the NCI xxxx web site on the internet, at www.nih.gov/xxxx. The web site contains the present report and a running account of modifications to IREP after installation, the IREP Users Guide, and instructions for running IREP from the web site.

(This page is a place-holder for material to be provided once installation has taken place.)