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Health Risks From Exposure to Low Levels of Ionizing Radiation

BEIR VII–Phase 2

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation

Board on Radiation Effects Research
Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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BACKGROUND

This is the seventh in a series of reports from the National Research Council prepared to advise the U.S. government on the relationship between exposure to ionizing radiation and human health. In 1996 the National Academies (NAS) was requested by the U.S. Environmental Protection Agency to initiate a scoping study preparatory to a new review of the health risks from exposure to low levels of ionizing radiations. The main purpose of the new review would be to update the Biological Effects of Ionizing Radiation V (BEIR V) report (NRC 1990), using new information from epidemiologic and experimental research that has accumulated during the 10 years since the 1990 review. Analysis of those data would help to determine how regulatory bodies should best characterize risks at the doses and dose rates experienced by radiation workers and members of the general public. BEIR VII-phase 1 was the preliminary survey to evaluate whether it was appropriate and feasible to conduct a BEIR VII-phase 2 study. The phase 1 study determined that it was appropriate and feasible to proceed to a phase 2 study. The phase 1 study, Health Effects of Exposure to Low Levels of Ionizing Radiations: Time for Reassessment?, published in 1998, also provided the basis for the phase 2 Statement of Task that follows:

BEIR VII PHASE 2 STATEMENT OF TASK

The primary objective of the study is to develop the best possible risk estimate for exposure to low-dose, low-linear energy transfer (LET) radiation in human subjects. In order to do this, the committee will 1) conduct a comprehensive review of all relevant epidemiologic data related to the risk from exposure to low-dose, low-LET radiation; 2) define and establish principles on which quantitative analyses of low-dose and low dose-rate effects can be based, including requirements for epidemiologic data and cohort characteristics; 3) consider relevant biologic factors (such as the dose- and dose-rate effectiveness factor, relative biologic effectiveness, genomic instability, and adaptive responses) and appropriate methods to develop etiologic models (favoring simple as opposed to complex models) and estimate population detriment; 4) assess the current status and relevance to risk models of biologic data and models of carcinogenesis, including critical assessment of all data that might affect the shape of the response curve at low doses, in particular, evidence for or against thresholds in dose-response relationships and evidence for or against adaptive responses and radiation hormesis; 5) consider when appropriate potential target cells and problems that might exist in determining dose to the target cell; and 6) consider any recent evidence regarding genetic effects not related to cancer. In performing the above tasks, the committee should consider all relevant data, even if obtained from high radiation exposures or at high dose rates.

With respect to modeling, the committee will 1) develop appropriate risk models for all cancer sites and other outcomes for which there is adequate data to support a quantitative estimate of risk, including benign disease and genetic effects; 2) provide examples of specific risk calculations based on the models and explain the appropriate use of the risk models; 3) describe and define the limitations and uncertainties of the risk

models and their results; 4) discuss the role and effect of modifying factors, including host (such as individual susceptibility and variability, age, and sex), environment (such as altitude and UV), and lifestyle (such as smoking history and alcohol consumption) factors; and 5) identify critical gaps in knowledge that should be filled by future research.

WHAT HAS CHANGED SINCE THE LAST BEIR REPORT ON THE HEALTH EFFECTS OF LOW LEVELS OF LOW-LET IONIZING RADIATION

In the 15 years since the publication of the previous BEIR report on Low LET radiation (BEIR V) much new information has become available on the health effects of ionizing radiation. Since the 1990 BEIR V report, substantial new information on radiation-induced cancer has become available from the Hiroshima and Nagasaki survivors, slightly less than half of whom were alive in 2000. Of special importance is the cancer incidence data from the Hiroshima and Nagasaki tumor registries. The committee evaluated nearly 13,000 incidence cancers and approximately 10,000 cancer deaths in contrast to fewer than 6000 cancer deaths available to the BEIR V committee. Also, since completion of the 1990 report, additional evidence has emerged from studies of the Hiroshima and Nagasaki bomb survivors suggesting that other health effects, such as cardiovascular disease and stroke, can result from radiation exposure.

A major reevaluation of the dosimetry at Hiroshima and Nagasaki has recently been completed that lends more certainty to dose estimates and provides increased confidence in the relationship between radiation exposure and health effects observed in the Japanese A-bomb survivors. Additional new information is also available from radiation-worker studies, medical-radiation exposures, and populations with environmental exposures.

Although the cancer risk estimates have not changed greatly since the 1990 report, confidence in the estimates has risen because of the increase in epidemiologic and biological data available to the committee.

Progress has also been made since the 1990 report in areas of science that relate to the estimation of genetic (hereditary) effects of radiation. In particular (a) advances in human molecular biology have been incorporated into the conceptual framework of genetic risk estimation and (b) it has become possible to project risks for all classes of genetic diseases, i.e., those with more complex as well as simple patterns of inheritance.

Advances in cell and molecular biology have also contributed new information on the mechanisms through which cells respond to radiation-induced damage and to the close associations between DNA damage response and cancer development.

ORGANIZATION OF THE STUDY

The National Research Council appointed a committee comprised of scientists and educators. Some had particular expertise in conducting research on ionizing radiation, while others were experienced in fields relevant to the Committee's charge. The NRC vetted all potential members to assure that each was free from any apparent or potential conflict of interest. The work of the committee was conducted with the assistance of the Board of Radiation Effects Research (BRER) of the Division on Earth and Life Sciences.

The Committee held 11 meetings over a period of 4.5 years. The long time duration of the Committee was largely due to a period of reduced activity while awaiting completion of the update of the dosimetry and exposure estimates to atomic bomb survivors of Hiroshima and Nagasaki, Japan (the so-called DS-02: Dosimetry System, 2002).

Six of the meetings included participation from the public for a portion of the meeting, and five of the meetings were conducted exclusively in executive session. Each meeting included extensive deliberations involving the Committee as a whole; in addition, two major subcommittees were formed that were termed "biology" and "epidemiology". Dr. Monson convened the epidemiology sessions and Dr. Cleaver convened the biology sessions. Also, a number of loosely organized and non-permanent working groups were formed to discuss the many issues before the Committee. This enabled biologists and non-biologists to work together and to evaluate each other's work.

ORGANIZATION OF THE REPORT

As noted under our STATEMENT OF TASK, our focus was to develop the best possible risk estimate for exposure to low-dose, low-LET radiation in human subjects. Accordingly, chapters 1-4 discuss basic aspects of radiation physics and radiation biology, including the known interaction between radiation exposure and genetic material, cellular structures, and whole organisms. Chapters 5-9 discuss basic principles of epidemiology as well as substantive data relating to exposure from the atomic bombs, medical radiation, occupational radiation, and environmental radiation. Chapters 10-12, to the extent possible, integrate the information from biology and epidemiology and develop risk estimates based on this information. Three summary sections provide different levels of description of the report. Chapter 13 is an overall scientific summary and lays out the Research Needs that the Committee has identified. The Executive Summary is an abbreviated and reorganized version of Chapter 13 that provides an overview of the report. The Public Summary addresses the findings of the Committee as well as how the report is relevant to public concerns about exposure to ionizing radiation.

REVIEWERS

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purposes of this review are to provide candid and critical comments that will assist the institution in making the published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their participation in the review of this report:

Seymour Abrahamson, University of Wisconsin, Madison, WI
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by George M. Hornberger, Ernest H. Ern Professor of Environmental Sciences & Associate Dean for the Sciences, University of Virginia, and John C. Bailer, III, Professor Emeritus, University of Chicago. Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the National Research Council.

GENERAL ACKNOWLEGEMENTS

The Committee thanks the Directors and Staff of the Radiation Effects Research Foundation, Hiroshima, Japan for providing the most current Life Span Study data on the Japanese atomic-bomb survivors. These data continue to be the primary source of epidemiologic information on the relationship between exposure to ionizing radiation and

its effects on human health. In particular, Dr. Donald Pierce was especially helpful in communication between RERF and the Committee; also, he added his insightful experience to the work of the Committee.

The Committee was aided in its consideration of its charge not only by comments from the public but also by formal presentations by experts from a number of fields. The following presentations were made as part of the public portion of the meetings (in order of appearance):

Presentations by Sponsors
Jerome Puskin, Ph.D.
Environmental Protection Agency

Vincent Holahan, Ph.D.
US Nuclear Regulatory Commission

Bonnie Richter, Ph.D.
US Department of Energy

Scientific speakers
John Boice, Ph.D.
International Epidemiology Institute
Epidemiology that should be considered by BEIR VII.

Charles Waldren, Ph.D.
Colorado State University
Adaptive effects, genomic instability, and bystander effects.

John Ward, Ph.D.
University of California San Diego
Differences between ionizing-radiation-induced DNA damage and endogenous oxidative damage.

Antone Brooks, Ph.D.
Washington State University Tri-cities
Overview of projects funded by the DOE low-dose program.

Charles Land, Ph.D.
National Institute of Health
NCI's update of the 1985 NIH Radioepidemiologic Tables.

L.B. Russell, Ph.D.
Oak Ridge National Laboratory
Early information derived from radiation-induced mutations in mice.

R. Chakraborty, Ph.D.
University of Texas School of Public Health
Mini- and microsatellite mutations and their possible relevance for genetic risk estimation.

Allan Balmain, Ph.D.
University of California, San Francisco
High and low penetrance genes involved in cancer incidence.

Al Fornace, Ph.D.
Harvard School of Public Health
Functional genomics and informatics approaches to categorize radiation response.

Steve Wing, Ph.D.
University of North Carolina
The relevance of occupational epidemiology to radiation risk assessment.

Edward Calabrese, Ph.D.
University of Massachusetts
Radiation hormesis.

David Utterback, Ph.D.
National Institute of Occupational Safety & Health
Exposure Assessment and Radiation Worker Studies.

Sharon Dunwoody, Ph.D.
University of Wisconsin
Challenges in the Communication of Scientific Uncertainties.

Suresh Moolgavkar, Ph.D., M.B.B.S.
School of Public Health and Community Medicine at the University of Washington and the Fred Hutchinson Cancer Research Center
Biology-based models.

We thank these presenters and all other members of the public who spoke on issues related to ionizing radiation.

We thank Doris Taylor and Cathie Berkley for their administrative assistance in assuring that the members of the Committee showed up at the right place at the right time. We also were aided in the work of the Committee by a talented group of Program Assistants. We thank Courtney Gibbs for her assistance in the preparation of this manuscript. We thank Courtney Slack, a Christine Mirzayan Science and Technology Policy Graduate Fellow who provided additional valuable assistance to NRC staff.

We thank Dr. Evan Douple for pulling us in and for holding us together. His wise and patient counsel along with his gentle encouragement, when needed, kept the Committee focused on its charge.

Finally, special thanks are due to Dr. Rick Jostes, the Study Director. His scientific expertise, persistence, equanimity, and organizational skills were essential to our staying the course.

RICHARD MONSON, *chairman*

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Units Used to Express Radiation Dose

Radiation exposures are measured in terms of the quantity *absorbed dose,* which equals the ratio of energy imparted to the mass of the exposed body or organ. The unit of absorbed dose is joule/kilogram (J/kg). For convenience this unit has been given the special name gray (Gy).

Ionizing radiation can consist of electromagnetic radiation, such as x rays or gamma rays (γ rays), or of sub-atomic particles, such as protons, neutrons, and α particles. X and γ rays are said to be sparsely ionizing, because they produce fast electrons which cause only a few dozen ionizations when they traverse a cell. Because the rate of energy transfer is called *linear energy transfer* (*LET*), they are also termed *low-LET* radiation; *low-LET* radiations are the subject of this report. In contrast, the heavier particles are termed *high-LET* radiations, because they transfer more energy per unit length as they traverse the cell.

Since the high-LET radiations are capable of causing more damage per unit absorbed dose, a weighted quantity, *equivalent dose,* or its average over all organs, *effective dose,* is used for radiation protection purposes. For low-LET radiations, *equivalent dose* equals *absorbed dose.* For high-LET radiation – such as neutrons, α particles or heavier ion particles – *equivalent dose* or *effective dose* equals the *absorbed dose* multiplied by a factor – the *quality factor* or the *radiation weighting factor* (see report glossary) – to account for their increased effectiveness. Since the weighting factor for radiation quality is dimensionless, the unit of *equivalent dose* is also J/kg. However, to avoid confusion between the two dose quantities, the special name sievert (Sv) has been introduced for use with *equivalent dose* and *effective dose.*

Although the BEIR VII report is about low-LET radiation, the committee had to consider information derived from complex exposures – especially from the A-bomb radiation – that include in addition to the low-LET radiation also a high-LET contribution. A *weighted dose,* with a weight factor that differs from the quality factor and the radiation weighting factor is employed in these computations. The symbol Sv for the unit is used likewise with this quantity.

Whenever the nature of the quantity is apparent from the context the term *dose* is used equally in this report for *absorbed dose, equivalent dose, effective dose,* and *weighted dose.* With regard to risk assessment, reference is usually to the *equivalent dose* to specified organs or to the *effective dose.* The symbol Sv for the unit is then used, although absorbed dose and equivalent dose are equal for low-LET radiation. In experimental radiation biology and in radiotherapy exact specification of absorbed dose is required and the dose values are frequently larger than in radiation protection considerations. With reference to those fields, therefore, use is made of absorbed dose and the symbol Gy for the unit.

The Public Summary refers to radiation protection, and the dose unit, therefore, is given as Sv throughout this section (for a more complete description of the various dose quantities and units used in the BEIR VII report, see the report glossary and the Units of Dose Table below).

Units of Dose

Unit[a]	Symbol	Conversion Factors
becquerel (SI)	Bq	1 disintegration/s = 2.7×10^{-11} Ci
curie	Ci	3.7×10^{10} disintegrations/s = 3.7×10^{10} Bq
gray (SI)	Gy	1 J/kg = 100 rad
rad	rad	0.01 Gy = 100 erg/g
sievert (SI)	Sv	1 J/kg = 100 rem
rem	rem	0.01 Sv

[a] International Units are designated SI.

Note: Equivalent dose equals absorbed dose times Q (quality factor). Gray is the special name of the unit J/kg to be used with absorbed dose; sievert is the special name of the unit J/kg to be used with equivalent dose

WHAT BODIES OF RESEARCH THE COMMITTEE REVIEWED

The Committee and staff ensured that BEIR VII's conclusions were informed by a thorough review of published, peer-reviewed materials relevant to the Committee's formal Statement of Task. Specifically, the sponsors of this study asked for a comprehensive review of all relevant epidemiologic data (*i.e.*, data from studies of disease in populations) related to health effects of low doses of ionizing radiation. In addition, the Committee was asked to review all relevant biological information important to the understanding or modeling of those health effects. Along with the review of these bodies of literature and drawing upon the accumulated knowledge of the Committee, the Committee members and staff also considered mailings, publications, and emails sent to them. Data on cancer mortality and incidence from the Life Span Study cohort of atomic bomb survivors in Hiroshima and Nagasaki, based on improved dose estimates, were used by the Committee. The Committee also considered radiation-risk information from studies of persons exposed for medical, occupational, and environmental reasons. Models for breast and thyroid cancer drew directly on medical studies. Further information was gathered in open sessions of the committee held at meetings in Washington, DC, and in Irvine, California. Questions and concerns raised in open sessions were considered by Committee members in the writing of this report.

Why has the committee not accepted the view that low doses are substantially more harmful than estimated by the linear no-threshold model?

Some of the materials the Committee reviewed included arguments that low doses of radiation are more harmful than a linear, no-threshold model of effects would suggest. The BEIR VII Committee concluded that radiation health effects research, taken as a whole, does not support this view. In essence, the BEIR VII Committee said that the higher the dose, the greater the risk; the lower the dose, the lower the likelihood of harm to human health. There are several intuitive ways to think about the reasons for this conclusion. First, any single track of ionizing radiation has the potential to cause cellular damage. However, if there is only one ionizing particle passing through a cell's DNA, the chances of damage to that cell's DNA are proportionately lower than if there are 10, 100 or 1000 such ionizing particles passing through it. There is no reason to expect a greater effect at lower doses from the physical interaction of the radiation with the cell's DNA.

New evidence from biology suggests that cells do not necessarily have to be hit directly by a radiation track for the cell to be affected. Some speculate that hit cells communicate with non-hit cells with chemical signals or by other means. To some this suggests that, at very low radiation doses, where all of the cells in the body are not hit, "bystander" cells may be adversely affected, resulting in a greater health effect at low doses than would be predicted by extrapolating the observed response at high doses. Others believe that increased cell death caused by "bystander" effects might lower the risk of

cancer by eliminating cells at risk for cancer from the irradiated cell population. While additional research needs to be done on the subject, it is unclear at this time whether the so-called "bystander" effect would have a net positive or net negative effect on the health of an irradiated person.

In sum, the total body of relevant research for the assessment of radiation health effects provides compelling reasons to believe that the risks associated with low doses of low-LET radiation are no greater than expected on the basis of the linear, no-threshold model.

Why has the committee not accepted the view that low doses are substantially less harmful than estimated by the linear no-threshold model?

In contrast to the previous section's subject, some materials provided to the Committee suggest that the LNT model exaggerates the health effects of low levels of ionizing radiation. They say that the risks are smaller than predicted by the LNT, are nonexistent, or that low doses of radiation may even be beneficial. The Committee also does not accept this hypothesis. Instead, the Committee concludes that the preponderance of information indicates that there will be some risk, even at low doses. As the simple risk calculations in this Public Summary show, the risk at low doses will be small. Nevertheless, the Committee's principal risk model for solid tumors predicts a linear decrease in cancer incidence with decreasing dose.

Before coming to this conclusion, the BEIR VII Committee reviewed articles arguing that a threshold or decrease in effect does exist at low doses. That is, those reports claimed that at very low doses ionizing radiation does not harm human health or may even be beneficial. Those reports were found either to be based on ecologic studies or to cite findings not representative of the overall body of data.

Ecologic studies assess broad regional associations, and in some cases, such studies have suggested that the incidence of cancer is well above or below numbers seen with more precise epidemiologic studies. When the complete body of research on this question is considered, a consensus view emerges. That view says that health risks of ionizing radiation, while small at low doses, are a function of dose.

Both the epidemiologic data and the biological data are consistent with a linear model at doses where associations can be measured. The main studies establishing the health effects of ionizing radiation are those analyzing survivors of the Hiroshima and Nagasaki atomic bombings in 1945. Sixty-five percent of these survivors received a low dose of radiation; that is, low according to the definition used in this report (equal to or less than 100 mSv). The arguments for thresholds or beneficial health effects are not supported by these data. Other work in epidemiology also supports the view that the harmfulness of ionizing radiation is a function of dose. Further, studies of cancer in children following exposure *in utero* or in early life indicate that radiation-induced cancers can occur at low doses. For example, the Oxford Survey of Childhood Cancer, found a "40

percent increase in the cancer rate among children up to [age] 15[21]." This increase was detected at radiation doses in the range of 10 to 20mSv.

There is also compelling support for the linearity view on how cancers form. Studies in radiation biology show that "a single radiation track (resulting in the lowest exposure possible) traversing the nucleus of an appropriate target cell has a low but finite probability of damaging the cell's DNA."[22] Subsets of this damage, such as ionization "spurs" that can cause multiple damages in a short length of DNA, may be difficult for the cell to repair or may be repaired incorrectly. The Committee concluded that there is no compelling evidence to indicate a dose threshold below which the risk of tumor induction is zero.

CONCLUSIONS

Despite the challenges associated with understanding the health effects of low doses of low LET radiation, current knowledge allows several conclusions. The BEIR VII Committee concludes that the current scientific evidence is consistent with the hypothesis that there is a linear dose-response relationship between exposure to ionizing radiation and the development of radiation-induced solid cancers in humans. The Committee further judges that it is unlikely that a threshold exists for the induction of cancers but notes that the occurrence of radiation-induced cancers at low doses, will be small. The Committee maintains that other health effects (such as heart disease and stroke) occur at high radiation doses but that additional data must be gathered before an assessment of any possible dose response can be made of connections between low doses of radiation and non-cancer health effects. Additionally, the Committee concludes that although adverse health effects in children of exposed parents (attributable to radiation-induced mutations) have not been found, there are extensive data on radiation-induced transmissible mutations in mice and other organisms. There is therefore no reason to believe that humans would be immune to this sort of harm.

[21] As noted on p. 71 in Cox, R., Muirhead, C. R., Stather, J. W., Edwards, A. A., and Little, M. P. 1995. Risk of radiation-induced cancer at low doses and low dose rates for radiation protection purporses. Documents of the [British] National Radiological Protection Board, Vol. 6, No. 1.

[22] As noted on p. 74 Cox, R., Muirhead, C.R., Stather, J.W., Edwards, A.A., and Little, M.P. 1995. Risk of radiation-induced cancer at low doses and low dose rates for radiation protection purposes. Documents of the National Radiological Protection Board, Vol. 6, No. 1.

- The choice of models for the transport of cancer risk from Japanese A-bomb survivors to the US population is influenced by mechanistic knowledge and information on the etiology of different cancer types.

- A combined Bayesian analysis of A-bomb epidemiologic information and experimental data has been developed to provide an estimation of the dose and dose-rate effectiveness factor (DDREF) for cancer risk estimates reported in this study.

- Knowledge on adaptive responses, genomic instability, and bystander signaling among cells that may act to alter radiation cancer risk was judged to be insufficient to be incorporated in a meaningful way into the modeling of epidemiologic data.

- Genetic variation in the population is a potentially important factor in the estimation of radiation cancer risk. Modeling studies suggest that strongly expressing mutations that predispose humans to cancer are too rare to distort appreciably population-based estimates of risk, but are a significant issue in some medical radiation settings.

- The estimation of the heritable effects of radiation takes advantage of new information on human genetic disease and on mechanisms of radiation-induced germ line mutation. The application of a new approach to genetic risk estimation leads the Committee to conclude that low-dose induced genetic risks are very small when compared to baseline risks in the population.

- The Committee judges that the balance of evidence from epidemiologic, animal and mechanistic studies tend to favor a simple proportionate relationship at low doses between radiation dose and cancer risk. Uncertainties on this judgment are recognized and noted.

Each of the above points contributes to refining earlier risk estimates, but none leads to a major change in the overall evaluation of the relation between exposure to ionizing radiation and human health effects.

ESTIMATING CANCER RISKS

As in past risk assessments, the LSS cohort of survivors of the atomic bombings in Hiroshima and Nagasaki plays a principal role in developing the Committee's recommended cancer risk estimates. Risk models were developed primarily from cancer incidence data for the period 1958-98 and based on DS02 dosimetry, the result of a major international effort to reassess and improve survivor dose estimates. Data from studies involving medical and occupational exposure were also evaluated. Models for estimating risks of breast and thyroid cancer were based on pooled analyses that included both data on both the LSS and medically exposed persons.

To use models developed primarily from the LSS cohort for the estimation of lifetime risks for the US population, it was necessary to make several assumptions that involve uncertainty. Two important sources of uncertainty are 1) the possible reduction in risk for exposure at low doses and dose rates, *i.e.*, the Dose and Dose-Rate Effect Factor (DDREF) and 2) the use of risk estimates based on Japanese atomic bomb survivors for estimating risks for the US population.

The committee has developed and presented in the text the committee's best possible risk estimates for exposure to low-dose, low-LET radiation in human subjects. As an example, Table ES-1 shows the estimated number of incident cancer cases and deaths that would be expected to result if a population of 100,000 persons with an age distribution similar to that of the entire US population were each exposed to 0.1 Gy, and also shows the numbers that would be expected in the absence of exposure. Results for solid cancers are based on linear models and reduced by a DDREF of 1.5. Results for leukemia are based on a linear-quadratic model.

The estimates are accompanied by 95% subjective confidence intervals (*i.e.* random as well as judgmental) that reflect the most important uncertainty sources, namely, statistical variation, uncertainty in the factor used to adjust risk estimates for exposure at low doses and dose rates, and uncertainty in the method of transport. The committee also presents in the text of the report example estimates for each of several specific cancer sites and other exposure scenarios, although they are not shown here.

TABLE ES-1 The Committee's preferred estimates of the lifetime attributable risk (LAR) of incidence and mortality for all solid cancers and for leukemia with 95% subjective confidence intervals. Number of cases or deaths per 100,000 exposed persons.

	All solid cancer		Leukemia	
	Males	Females	Males	Females
Excess cases (including non-fatal cases) from exposure to 0.1 Gy	800 (400, 1600)	1300 (690, 2500)	100 (30, 300)	70 (20, 250)
Number of cases in the absence of exposure	45,500	36,900	830	590
Excess deaths from exposure to 0.1 Gy	410 (200, 830)	610 (300, 1200)	70 (20, 220)	50 (10, 190)
Number of deaths in the absence of exposure	22,100	17,500	710	530

In general the magnitude of estimated risks for total cancer mortality or leukemia has not changed greatly from estimates provided in past reports such as BEIR V and recent UNSCEAR and ICRP reports. New data and analyses have reduced sampling uncertainty, but uncertainties related to estimating risk for exposure at low doses and dose rates and to transporting risks from Japanese A-bomb survivors to the U.S. population remain large. Uncertainties in estimating risks of site-specific cancers are especially large.

As an illustration, Figure ES-1 shows estimated excess relative risks (ERR) of solid cancer versus dose (averaged over sex, and standardized to represent individuals exposed at age 30 and at attained age 60), for atomic bomb survivors with doses in each of 11 dose intervals less than 2.0 Sv. The figure in the insert represents ERR vs. dose for leukemia.

This plot conveys the overall dose-response relationship from the LSS cohort and its role in low-dose risk estimation. It is important to note that the difference between the linear and linear-quadratic models in the low-dose ranges is small relative to the error bars; therefore, the difference between these models is small relative to the uncertainty in the risk estimates produced from them. For solid cancer incidence the linear-quadratic model did not offer statistically significant improvement in the fit, so the linear model was used. For leukemia, a linear-quadratic model (insert figure ES-1) was used since it fitted the data significantly better than the linear model.

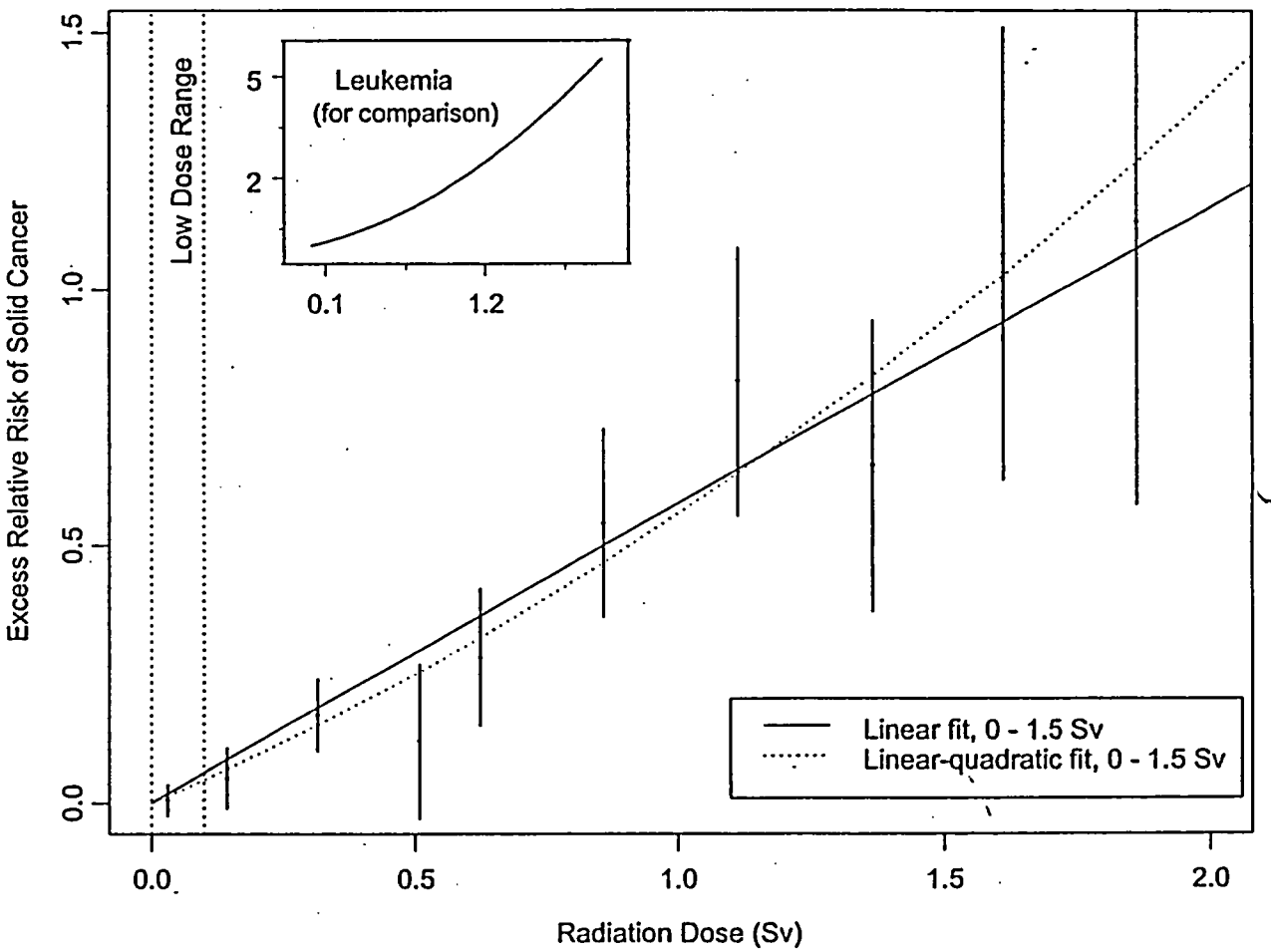

FIGURE ES-1. Excess Relative Risks of Solid Cancer for the Japanese Atomic Bomb Survivors. The plotted points are the estimated excess relative risks of solid cancer incidence (averaged over sex, and standardized to represent individuals exposed at age 30 and at attained age 60) for atomic bomb survivors with doses in each of 10 dose intervals, plotted above the midpoints of the dose intervals. If R(d) represents the age-specific instantaneous risk at some dose d, then the *excess relative risk* at dose d is [R(d) – R(0)]/R(0) (which is necessarily zero when dose is zero). The vertical lines are

approximate 95% confidence intervals. The solid and dotted lines are estimated linear and linear-quadratic models for excess relative risk, estimated from all subjects with doses in the range 0 to 1.5 Sv. (These are not estimated from the points; but from the lifetimes and doses of the individual survivors, using statistical methods discussed in Chapter 6). A linear-quadratic model will always fit the data better than a linear model, since the linear model is a restricted special case with quadratic coefficient equal to zero. For solid cancer incidence, however, there is no *statistically significant* improvement in fit due to the quadratic term. It should also be noted that in the low dose range of interest the difference between the estimated linear and linear-quadratic models is small relative to the 95% confidence intervals. The insert shows the fit of a linear-quadratic model for leukemia, to illustrate the greater degree of curvature observed for that cancer.

CONCLUSION

The Committee concludes that the current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans.

BEIR VII RECOMMENDED RESEARCH NEEDS

A more detailed listing of the BEIR VII recommended research needs is found at the end of Chapter 13.

Research Need 1. Determination of the level of various molecular markers of DNA damage as a function of low dose ionizing radiation.

Currently identified molecular markers of DNA damage and other biomarkers that can be identified in the future should be used to quantify low levels of DNA damage and to identify the chemical nature and repair characteristics of the damage to the DNA molecule.

Research Need 2. Determination of DNA repair fidelity, especially as regards double and multiple strand breaks at low doses, and whether repair capacity is independent of dose.

Repair capacity at low levels of damage needs to be investigated, especially in light of conflicting evidence for stimulation of repair at low doses. In these studies the accuracy of DNA sequences rejoined by these pathways needs to be determined, and the mechanisms of error-prone repair of radiation lesions need to be elucidated.

Research Need 3. Evaluation of the relevance of adaptation, low-dose hypersensitivity, bystander effect, hormesis, and genomic instability for radiation carcinogenesis.

Mechanistic data are needed to establish the relevance of these processes to low dose radiation exposure, *i.e.* <100 mGy. Relevant end points should include not only chromosomal aberrations and mutations but also genomic instability and induction of cancer. *In vitro* and *in vivo* data are needed for delivery of low doses over several weeks or months at very low dose rates or with fractionated exposures. The cumulative effect of

multiple low doses of less than 10 mGy delivered over extended periods needs to be explored further. The development of *in vitro* transformation assays utilizing non-transformed human diploid cells is judged to be of special importance.

Research Need 4. Identification of molecular mechanisms for postulated hormetic effects at low doses.

Definitive experiments that identify molecular mechanisms are needed to establish whether hormetic effects exist for radiation-induced carcinogenesis.

Research Need 5. Tumorigenic Mechanisms

Further cytogenetic and molecular genetic studies are needed to reduce current uncertainties on the specific role of radiation in multi-stage radiation tumorigenesis.

Research Need 6. Genetic factors in radiation cancer risk.

Further work is needed in humans and mice on gene mutations and functional polymorphisms that influence radiation response and cancer risk.

Research need 7. Heritable genetic effects of radiation

Further work is needed to establish (a) the potential roles of DNA double strand break (DSB) repair processes in the origin of deletions in irradiated stem cell spermatogonia and oocytes (the germ cell stages of importance in risk estimation) in mice and humans and (b) the extent to which large radiation-induced deletions in mice are associated with multi-system development defects. In humans, the problem can be explored using genomic databases and knowledge of mechanisms of origin of radiation-induced deletions to predict regions that may be particularly prone to radiation-inducible deletions.

With respect to epidemiology, studies on genetic effects of radiotherapy for childhood cancer, should be encouraged, especially when they can be coupled with modern molecular techniques (such as array-based comparative genomic hybridization).

Research Need 8. Future medical radiation studies.

Most studies of medical radiation should rely on exposure information collected prospectively, including cohort studies as well as nested case-control studies. Future studies should continue to include individual dose estimation to the site of interest, as well as an evaluation of the uncertainty in the dose estimation.

Studies of populations with high and moderate dose medical exposures are particularly important for the study of modifiers of radiation risks. Because of the high level of radiation exposure in these populations, they are also ideally suited to study the effects of gene-radiation interactions, which may render particular subsets of the population more sensitive to radiation-induced cancer. Genes of particular interest include BRCA1, BRCA2, ATM, CHEK2, NBS1, XRCC1, and XRCC3.

Of concern for radiological protection is the increasing use of computed tomography (CT) scans and diagnostic X rays. Epidemiologic studies of the following exposed populations, if feasible, would be particularly useful: (1) Follow-up studies of

persons receiving CT scans, especially children; (2) Studies of infants who experience diagnostic exposures related to cardiac catheterization, those who have recurrent exposures to follow their clinical status, and premature babies monitored for pulmonary development with repeated X rays.

There is a need to organize worldwide consortia that would use similar methods in data collection and follow-up. These consortia should record delivered doses and technical data from all x ray or isotope-based imaging approaches including CT, positron emission tomography (PET), and Single Photon Emission Computed Tomography (SPECT).

Research Need 9. Future occupational radiation studies.

Studies of occupational radiation exposures, in particular among nuclear industry workers, including nuclear power plant workers, are well suited for the direct assessment of the carcinogenic effects of long-term, low-level radiation exposure in humans. Ideally, studies of occupational radiation should be prospective in nature, and rely on individual real time estimates of radiation doses. Where possible, national registries of radiation exposure to workers should be established and updated as additional radiation exposure is accumulated and as workers change employers. These registries should include at least annual estimates of whole-body radiation dose from external photon exposure. These exposure registries should be linked with mortality registries and, where they exist, national tumor (and other disease) registries. It is also important to continue follow-up of workers exposed to relatively high doses, that is, workers at the Mayak nuclear facility and workers involved in Chernobyl clean-up.

Research Need 10. Future environmental radiation studies.

In general, additional ecologic studies of persons exposed to low levels of radiation from environmental sources are not recommended. However, if there are disasters where a local population is exposed to unusually high levels of radiation, it is important that there be a rapid response not only for prevention of further exposure but also for establishment of scientific evaluation of the possible effects of the exposure. The data collected should include basic demographic information on individuals, estimates of acute and possible continuing exposure, the nature of the ionizing radiation, and the means of following these individuals for many years. The possibility of enrolling a comparable non-exposure population should be considered. Studies of persons exposed environmentally as a result of the Chernobyl disaster or as a result of releases from the Mayak nuclear facility should continue.

Research Need 11. Japanese Atomic-bomb survivor studies.

The Life Span Study cohort of Japanese A-bomb survivors has played a central role in BEIR VII and in past risk assessments. It is important that follow-up for mortality and cancer incidence continue for the 45% of the cohort who remained alive at the end of 2000.

In the near future, an uncertainty evaluation of the DS02 dosimetry system is expected to become available. Dose-response analyses that make use of this evaluation should thus be conducted to account for dosimetry uncertainties.

Development and application of analytic methods that allow more reliable estimation of site-specific estimates is also needed. Specifically, methods that draw on both data for the specific site and data on broader cancer categories could be useful.

Research Need 12. Epidemiologic studies in general

Data from the Life Span Study cohort of A-bomb survivors should be supplemented with data on populations exposed to low doses and/or dose rates, especially those with large enough doses to allow risks to be estimated with reasonable precision. Studies of nuclear industry workers and careful studies of persons exposed in countries of the former Soviet Union are particularly important in this regard.

association was observed for all nervous system tumors with an estimated ERR per Sv of 1.2 (95% CI: 0.6, 2.1). The ERR per Sv was highest for Schwannomas [4.5 (95% CI 1.9, 9.2)], but the dose-response for all other central nervous system tumors evaluated as a group was also statistically significant. The dose-response for all nervous system tumors and for Schwannoma were both statistically significant when limited to subjects with doses of less than one Sv, and there was no evidence that the slope for this low-dose range was different from that for the full range. Modification of risk by sex, age at exposure, and attained age was also investigated.

NON-NEOPLASTIC DISEASE

Findings based on mortality data

A statistically significant dose-response relationship with mortality from non-neoplastic disease in A-bomb survivors was demonstrated by Shimizu and others (1992) based on mortality data for the period 1950-85. The addition of five years of mortality data (through 90) strengthened the evidence for this effect and allowed a more detailed evaluation (Shimizu and others 1999). In these analyses, statistically significant associations were seen for the categories of heart disease, stroke, and diseases of the digestive, respiratory and hematopoietic systems.

Preston and others (2003) updated these results further and present analyses of deaths from all causes excluding neoplasms, blood diseases, and external causes such as accidents or suicide. They give considerable attention to the fact that for a few years after the A-bomb explosions, baseline risks for non-cancers in proximal survivors (within 3000 m of the hypocenter) were markedly lower than those in distal survivors. They refer to this as the "healthy survivor effect", and note that it could lead to distortion of the dose-response particularly in the early years of follow-up. They also note that a small difference (2%) in baseline risks for proximal and distal survivors persisted in later years, which they consider likely to be due to demographic factors such as urban-rural differences. They address this potential source of bias by conducting analyses restricted to the period 1968-1997 and by including an adjustment for differences in proximal and distal survivors (although results without the adjustment are also presented).

The estimated ERR/Sv for non-cancers based on a linear model with no dependence on age at exposure or sex was 0.14, generally lower than that for all solid cancers (where the ERR/Sv depends on age and sex). There was no evidence of a statistically significant dependence on either age at exposure or sex, but the data were compatible with effects similar to those estimated for solid cancers. A linear dose-response function fitted the data well, but it was not possible to rule out a pure quadratic model or a model with a threshold as high as 0.5 Sv. Similar to Shimizu and others (1999), significant dose-response relationships were found for heart disease, stroke, respiratory disease, and digestive disease. There was no evidence of radiation effects for infectious diseases or all other non-cancer diseases in the group evaluated. Lifetime non-cancer risks for people exposed to one Sv were estimated to be similar to those for solid cancer for those exposed as adults, and about half those for solid cancer for those exposed as children. Because baseline risks for the non-cancer category evaluated are larger than those for all solid cancers, even the relatively small ERR/Sv leads to a fairly large absolute lifetime risk.

Because small ERRs can easily arise from bias, Shimizu and others (1999) evaluated several potential sources of bias including misclassification of cause of death, confounding, and cohort selection effects. Although Preston and others discuss cohort selection effects in detail, they did not reevaluate other sources of bias. We summarize the discussion provided by Shimizu and others in the remainder of this section.

With regard to misclassification, they note that Sposto and others (1992) investigated the possibility of bias from this source using mortality data through 1985. These investigators used estimated age-dependent misclassification probabilities obtained from RERF autopsy data to conduct analyses that corrected for misclassification, and found that estimates for non-cancer mortality were reduced by 20%, but remained highly statistically significant. Shimizu and others used mail survey and interview data to examine the possible effect of several potential confounders including educational history and smoking. Although most of the factors evaluated were found to affect non-cancer mortality, they were not found to be strongly associated with dose. Analyses adjusted for various confounders, based on survivors with available data, resulted in ERR/Sv that were very similar to the unadjusted values.

Shimizu and others also evaluated non-cancer diseases of the blood, benign neoplasms, and deaths from external causes. Because these categories were not reevaluated by Preston and others (2003), we summarize these findings. The ERR/Sv for the 191 deaths from non-cancer diseases of the blood was estimated to be 1.9 (90% CI 1.2, 2.9), larger than the estimated values for most solid cancers. The accuracy of death certificate diagnosis is known to be poor for this category and likely to include many misclassified leukemias and malignant lymphoma deaths. Among 128 deaths for which additional diagnostic information was available, there were 57 non-neoplastic disease deaths. When these deaths were analyzed separately the resulting ERR/Sv was 2.0 (90% CI 0.6, 4.4), nearly identical to that based on the full 191 deaths. Analyses suggested that the effect was limited to non-aplastic anemias (29 cases), since the estimate for aplastic anemias (31 cases) was essentially zero. There was also a suggestion of a strong dose response based on the 13 deaths from myelodysplastic syndrome, a neoplastic disease thought to be a precursor of acute myelogenous leukemia.

Although the data evaluated by Shimizu and others included 379 deaths attributed to benign neoplasms or neoplasms of unspecified nature, only 31 deaths were specifically indicated on the death certificate as being due to benign neoplasms. There was no convincing evidence of a dose-response for these 31 deaths.

With regard to deaths from external causes, suicide rates showed a statistically significant decline with increasing dose, whereas no evidence of a dose-response relationship was found for deaths from other external causes.

Findings based on the Adult Health Study (AHS) or on autopsy data

Wong and others (1993) evaluated the relationship between exposure to radiation and the incidence of 19 nonmalignant disorders using data from the Adult Health Study (AHS) cohort for the period 1958-1986. They found statistically significant positive dose-response relationships ($p < 0.05$) for thyroid disease ($p < 0.001$), chronic liver disease and cirrhosis ($p = 0.007$), and uterine myoma ($p < 0.001$). In addition, myocardial infarction showed a significant dose-response for the period 1968-86 among those who were under 40

years of age at exposure (p= 0.03). Statistically significant relationships were not detected for hypertension, hypertensive heart disease, ischemic heart disease, occlusion and stenosis of precerebral and cerebral arteries, aortic aneurysm, stroke, cataract, gastric ulcer, duodenal ulcer, viral hepatitis, calculus of kidney and ureter, cervical polyp, hyperplasia of prostate, dementia, and Parkinson's disease. Modification of the ERR/Sv by sex, city, age at exposure and time since exposure was also investigated for those endpoints showing overall associations. Age at exposure was found to be a significant modifier of risk for thyroid disease (decreasing ERR/Sv with increasing age); modifying effects for uterine myoma are discussed above (under Benign Neoplasms).

Kodama and others (1996) reviewed results of studies addressing non-cancer diseases and their relationship with radiation exposure in A-bomb survivors. They also updated some of the analyses by Wong and others (1993) to include data through 1990, but do not present nearly as much detail as Wong and others. They found a statistically significant association for myocardial infarction based on all the data (p = 0.02) with an estimated ERR/Sv of 0.17 (95% CI 0.01, 0.36). The association remained significant when analyses were adjusted for various risk factors including blood pressure and cholesterol. Positive dose-response relationships were also found for several other endpoints of atherosclerosis, which the authors interpreted as supporting a real association between radiation exposure and atherosclerosis. Kodama and others confirmed previously identified radiation associations for uterine myoma, hyperparathyroidism, and chronic liver disease with ERR/Gy of 0.46 (0.27, 0.70), 3.1 (0.7, 13), and 0.14 (0.04, 0.27) for the three respective endpoints.

Wong and others (1999) used AHS data to examine long-term trends in total serum cholesterol levels over the 28-year period 1958-1986. Dose-response relationships for the increase in cholesterol levels over time were demonstrated for women in general but only for the youngest birth cohort (1935-1945) for men. Age, body mass index, city, and birth year were considered in the analyses, and some analyses were adjusted for cigarette smoking. These results may partially explain the dose-response relationship for coronary heart disease that has been observed in other studies of atomic bomb survivors.

LIFE SHORTENING

Cologne and Preston (2000) investigated life shortening in the LSS cohort using mortality data through 1995. Although dose-related increases in both cancer and non-cancer mortality imply that longevity is also related to dose, earlier papers addressing these effects (Pierce and others 1996; Shimizu and others 1998) did not specifically attempt to quantify the degree of radiation-induced life shortening, an endpoint that reflects the effects of both cancer and non-cancer mortality. The investigation of longevity was undertaken in part because of earlier reports in both the scientific literature and in the press that certain atomic-bomb survivors had greater-than-average life expectancy.

A clear decrease in median life expectancy with increasing radiation dose was found. Among cohort members with estimated doses between 0.005 and 1.0 Gy, the median loss of life was estimated to be about two months, while among cohort members with estimated doses of one Gy or more, the median loss of life was estimated to be about 2.6 years. The median loss of life among all cohort members with doses estimated to be greater than zero was about four months.

Cologne and Preston (2000) present estimates of life expectancy for groups defined by dose. For those with zero dose, they present separate estimates for groups defined by distance from the hypocenter including estimates for those who were not in the city (>10 km from the hypocenter). Although the relative mortality for all non-zero dose groups compared with the combined in-city zero-dose group was 1.0 or greater, results for those in the lowest dose category (0.005 to 0.25 Gy) were somewhat dependent on the choice of comparison group. Cohort members in this low-dose category had median life expectancy that was shorter than the zero-dose survivors who were within three km of the hypocenter (229 days), shorter than the not-in-city group (365 days), but slightly longer (52 days) than survivors located three or more km from the hypocenter. These results do not support the hypothesis that life expectancy for atomic bomb survivors exposed at low doses is greater than for comparable unexposed persons.

SUMMARY OF A-BOMB SURVIVOR CHAPTER

The Life Span Study (LSS) cohort of survivors of the atomic bombings in Hiroshima and Nagasaki continues to serve as a major source of information for evaluating health risks from exposure to radiation, and particularly for developing quantitative estimates of risk from exposure to ionizing radiation. Its advantages include large size, the inclusion of both sexes and all ages, a wide range of doses that have been estimated for individual subjects, and high quality mortality and cancer incidence data. In addition, the whole body exposure received by this cohort offers the opportunity to assess risks for cancers of a large number of specific sites and to evaluate the comparability of site-specific risks. The full LSS cohort consists of approximately 120,000 persons who were identified at the time of the 1950 census. However, most recent analyses have been restricted to approximately 87,000 survivors who were in the city at the time of the bombings and for whom it is possible to estimate doses. Special studies of subgroups of the LSS have provided clinical data, biological measurements, and information on potential confounders or modifiers.

Mortality data for the period 1950-1997 have been evaluated in detail, adding 12 years to the follow-up period available at the time the BEIR V report was published. The longer follow-up period not only increases statistical precision, but also allows more reliable assessment of the long term effects of radiation exposure including modification or risk by attained age and time since exposure. Importantly, cancer incidence data from both the Hiroshima and Nagasaki tumor registries became available for the first time in the 1990s. These data not only include non-fatal cancers, but also offer diagnostic information that is of higher quality that that based on death certificates, especially important for evaluating site-specific cancers. Although published evaluations described in Chapter 6 are based on DS86 dosimetry, a revised DS02 system, which is the result of a major international effort to reassess and improve survivor dose estimates, has recently become available and was used to develop BEIR VII risk models. An initial evaluation indicates that this revision will slightly reduce risk estimates.

The more extensive data on solid cancer that are now available have allowed more detailed evaluation of several issues pertinent to radiation risk assessment. Several investigators have evaluated the shape of the dose-response focusing on the large number of survivors with relatively low doses. These analyses have generally confirmed the

appropriateness of linear functions to describe these data. The modifying effects of sex, age at exposure, and attained age have also been explored in detail using both excess relative risk (ERR) and excess absolute risk (EAR) models. The ERR per Sv has been found to decrease with both increasing age at exposure and increasing attained age, and it now appears that both variables may be needed to provide an adequate description of the data. By contrast, the EAR shows a sharp increase with increasing attained age and a decrease with increasing age at exposure.

The availability of high quality cancer incidence data has resulted in several analyses and publications addressing specific cancer sites. These analyses often include special pathological review of the cases and sometimes include data on additional variables (such as smoking for the evaluation of lung cancer risks). Papers focusing on the following cancer sites have been published in the last decade: female breast cancer, thyroid cancer, salivary gland cancer, liver cancer, lung cancer, skin cancer and central nervous system tumors. Special analyses have also been conducted of cancer mortality in survivors who were exposed either *in utero* or during the first five years of life.

Health endpoints other than cancer have been linked with radiation exposure in the LSS cohort. Of particular note, a dose-response relationship with mortality from non-neoplastic disease mortality was demonstrated in 1992 and in subsequent analyses in 1999 and 2003 have strengthened the evidence for this association. Statistically significant associations were seen for the categories of heart disease, stroke, and diseases of the digestive, respiratory and hematopoietic systems. The data were inadequate to distinguish between a linear dose-response, a pure quadratic response, or a dose-response with a threshold as high as 0.5 Sv.

CT scans

As indicated in the introduction to this chapter, there is concern about the potential health effect of repeated computed tomography (CT) scan exposures, particularly in childhood. No epidemiologic study of populations exposed to CT was available to the committee.

Brenner and others, 2001 and Brenner and Elliston, 2004 have evaluated the possible consequences of CT exposures based on estimated doses to specific organs. They concluded that lifetime risks of cancer are not negligible.

Exposure *in utero*

Prenatal x rays were first associated with increased risk of childhood leukemia and cancer in the 1950s in the Oxford Survey of Childhood Cancers (OSCC), a UK wide study started in 1955 (Stewart and others 1958). Results were based on a case-control study of 1416 childhood cancer deaths and the same number of controls, in which mothers of the study subjects were asked about their child's history of radiographic examinations (*in utero* and after birth). This association was confirmed by MacMahon (1962) in a study of a cohort of 734,243 children born in the Northeastern US between 1947 and 1954, in which 584 subjects had died of cancer in childhood and information about pre-natal x rays was obtained from medical records, thus eliminating the possibility of recall bias.

The Oxford Survey of Childhood Cancers is the largest study of childhood cancer after prenatal exposure to x rays. It has continued and been expanded to cover all children dying from malignant disease in the UK under the age of 16 (Bithell and Stewart 1975) (Knox and others, 1987; Gilman and others, 1989); in 1981, it included 15,276 matched case-control pairs. The magnitude of the association appears to have diminished over time (Muirhead and Kneale, 1989), but so has the dose of radiation to which pregnant women have been exposed during examinations (Doll and Wakeford 1997). A decrease over time also was reported in the Northeastern US study (Monson and MacMahon 1984).

The possible effect of pre-natal exposure has been studied in a number of other populations in the US and Europe. Results of the case-control studies have been combined in meta-analyses by Bithell (1989, 1990). Although results are dominated by the OSCC, results of these studies show a significant relative risk of 1.4 for *in utero* radiation in association with childhood cancer (Doll and Wakeford 1997).

Controversy continues, however, on the existence and size of the risk following pre-natal exposures. Boice and Miller (1999) noted that the increases were restricted to case-control studies and not seen in cohort studies; they also commented on the similarity of relative risks for leukemia and solid cancers, suggesting an underlying bias in the case-control studies. In their review, Doll and Wakeford (1997) discuss these arguments. In regard to cohort studies, they combine the results of cohort studies for which relative risks can be calculated reliably and note that, when the atomic bomb survivors are excluded, an increased risk is obtained that is consistent with the combined results of case-control studies. They note further that the incomplete follow-up of the Japanese atomic bomb survivor cohort in the years following the bombings may be partially responsible for the apparent inconsistency of results concerning the effects of pre-natal exposures. The argument that radiation risks of leukemia and solid cancers differ is based on observations of exposure in childhood and later years. Doll and Wakeford (1997) note that it is not

expected that the carcinogenic effects of radiation exposure *in utero* and in childhood would be the same, as the cells that give risk to most of the typical childhood cancers other than leukemia persist and are capable of dividing for only a short time, if at all, after birth. Doll and Wakeford further conclude that the idea that the relationship is causal is supported by the increase in relative risk with increasing number of x ray examinations conducted in the third trimester of pregnancy and the significant decline in relative risk with year of birth, paralleling the decline in fetal doses that occurred over the same period (UNSCEAR, 1972).

Based on the results of the Oxford Survey and the other studies of the effects of maternal irradiation, UNSCEAR (1996) reported a statistically significant leukemia risk (up to age 15 years) and estimated a 40% increase in risk of childhood cancers (up to 15 years) at doses of 10-20 mGy (low LET). Risk estimates have been derived since then by a number of authors and committees (UNSCEAR 1996; Doll and Wakeford 1997; Wakeford and Little 2003). In the most recent analyses, Wakeford and Little (2003), derive an ERR for childhood cancer following pre-natal exposure of about 50 per Gy, with an EAR risk of about 8% per Gy. They comment, however, that the statistical, dosimetric, modeling and other uncertainties associated with these risk estimates are appreciable. They note that when these uncertainties and those associated with equivalent risk coefficients from the Japanese atomic bomb survivor cohort exposed *in utero* are taken into account, the risk estimates for childhood cancer from these two sources of data are compatible and they conclude that: "... doses to the fetus *in utero* of the order of 10 mSv discernibly increase the risk of childhood cancer".

Diagnostic ^{131}I exposures

The use of ^{131}I for diagnostic purposes in childhood is rare and hence information on risk is very sparse. In the cohort of 34,104 patients who had received ^{131}I diagnostic exposures for suspected thyroid disorders in Sweden between 1951 and 1969 reported above by Hall and others (1996), only 2408 patients were under age 20 at the time of the examination. Among these, a small excess risk was seen (three cases observed vs. 1.8 expected).

Summary

Information on radiation risks following diagnostic radiation exposure in childhood come from a study of women who received multiple diagnostic x rays from the evaluation of scoliosis during childhood and adolescence. This study, in which important efforts were made to reconstruct dose to the breast, has provided an estimate of the risk of radiation-induced breast cancer. This estimate is reviewed and compared with risk estimates derived from other medical exposure studies, in the following section of this chapter "EVALUATION OF RISK FOR SPECIFIC CANCER SITES".

Studies of pre-natal exposure to diagnostic x rays have, despite a long-standing controversy, provided important information on the existence of a significantly increased risk of leukemia and childhood cancer following diagnostic doses of 10-20 mGy *in utero*.

Only one study has examined the effects of uses of ^{131}I for diagnostic purposes in childhood. A small excess of thyroid cancer risk was seen – based on very small numbers – and no risk estimate is provided.

Among the studies of populations with external radiation exposure and/or ^{226}Ra, the estimates of ERR per Gy range from negative (in the hemangioma study) to 1.3 per Gy in the study of benign breast disease. The confidence intervals are wide, and they all overlap, indicating that these estimates are statistically compatible. An ERR of 1.32 per Gy (not significantly different from zero) was seen among patients treated for hyperthyroidism with ^{131}I.

Radiation and circulatory diseases

Although radiation exposure is well established as a risk factor for cancer, a clear understanding of the relationship between radiation exposure and other diseases is lacking. It has been postulated that the cardiovascular system is resistant to radiation-induced injury (Stewert 1995). However, it appears that tissue damage may occur as a result of both therapeutic (Stewart and Fajardo 1984) and A-bomb radiation exposure (Villeneuve and Morrison. 1997; Shimizu and others 1999). Capillaries represent the most radiosensitive component of the cardiovascular system, with characteristic changes including detachment of endothelial cells and thrombosis. Arterial changes resulting from radiation exposure depend on vessel size, with small and medium-sized arteries undergoing changes in all vessel layers, and large arteries appearing to be relatively radioresistant; although, radiation exposure may predispose larger vessels to the development of atherosclerosis (Louis and others 1974).

Radiation exposure has also been implicated in the development of cerebrovascular injury (O'Connor and Mayberg 2000). Specific conditions postulated to arise from irradiation include vasculopathy, intracranial aneurysm formation, cerebral radiation necrosis, intracranial atherosclerosis, and stroke (Trivedi and Hannan, 2004).

Both animal and human studies have identified intimal thickening, lipid deposition, and adventitial fibroses of the vascular system following irradiation. These changes are associated with atherosclerosis and the normal aging process, although irradiation may accelerate the development of these conditions (Trivedi and Hannan, 2004).

Although the dose required to produce specific conditions or vascular effects is uncertain, it appears that over extended periods the nature of the changes induced are similar for low doses (on the order of five Gy) as for high doses (in the region of 40 Gy). There is a broad spectrum and severity of cardiovascular diseases, with radiation being only one of many possible risk factors that may act directly or indirectly on the vasculature. In order to clarify the role of radiation in the etiology of cardiovascular diseases further studies involving long-term low-level exposures are needed, taking into account all of the known risk factors for cardiovascular outcomes

Excess heart disease mortality has been observed among women with breast cancer who were irradiated with cobalt-60 (Host and Loeb 1986– not reviewed here) and among persons with Hodgkin disease who received mediastinal irradiation (Boivin and Hutchison 1982, Hancock and others 1993b,c). Most affected patients had received at least 30 Gy to the mediastinum, although some had received less (Trivedi and Hannan, 2004).

attained age (a). Since $t = a - e$, ERR (D, e, a) or ERR (D, e, a) are obtained by substituting $a - e$ for t in the models presented in Table 12-3. We further note that for the period 2-5 years after exposure, the excess absolute risk is assumed to be the same as that at five years following exposure. That is, for $a = e + 2$ to $e + 5$, M(D, e, a) = M(D, e, $e + 5$).

The approach described above for obtaining estimates based on absolute transport differs from that used by UNSCEAR (2000b) and NIH (2003), where M (D, e, a) for absolute risk transport was calculated by multiplying the ERR (D, e, a) estimated from the LSS data by sex- and age-specific baseline risks for the 1985 population of Japan. Because Japanese rates for cancer of several sites have changed in the period 1950-1985 (becoming more similar to US rates), our approach may reflect risks more truly in the LSS cohort than do 1985 baseline rates for Japan.

Another difference in our approach and that of UNSCEAR is that for estimating cancer incidence, UNSCEAR lifetime risk calculations counted only first cancers. That is, once a person was diagnosed with cancer (baseline or radiation-induced), they were removed from the population at risk. By contrast, our calculations count all primary cancers including those in persons previously diagnosed with another primary cancer.

To obtain estimates of risk for a population of mixed exposure ages, the age at exposure-specific estimates in equation 4 were weighted by the fraction of the population in the age group based on the US population in 1999 (http://wonder.cdc.gov/popu0.shtml). Estimates of chronic lifetime exposure are for a person at birth, with allowance for attrition of the population with age. These estimates are obtained by weighting the age at exposure-specific estimates by the probability of survival to each age, that is, S(e). Similarly, estimates for chronic occupational exposure are for a person who enters the workforce at age 18 and continues to be exposed to age 65, again with allowance for attrition of the population with age. These estimates are obtained by weighting the age at exposure-specific estimates by the probability of survival to each age conditional on survival to age 18, that is, S(e)/S(18).

QUANTITATIVE EVALUATION OF UNCERTAINTY IN LIFETIME RISKS

Because of the various sources of uncertainty it is important to regard specific estimates of lifetime attributable risk (LAR) with a healthy skepticism, placing more faith in a range of possible values. While a confidence interval is the usual statistical device for doing so, the approach here also accounts for uncertainties external to the data, treating subjective probability distributions for these uncertainties *as if* they resulted from real data. The resulting range of plausible values for lifetime risk is consequently labeled a "subjective confidence interval" to emphasize its dependence on opinions in addition to direct numerical observation. Similar logic has been used in other uncertainty analyses (NCRP 1997; EPA 1999; UNSCEAR 2000b).

The quantitative analysis focuses on the three sources that are thought to matter most: (1) sampling variability in risk model parameter estimates from the LSS data, (2) the uncertainty about transport of risk from a Japanese (LSS) to a US population (*i.e.* whether ERR or EAR is transportable), and (3) the uncertainty in the appropriate value of a dose and dose-rate effectiveness factor (DDREF) for adjusting low-dose risks based on linear-in-dose risk models estimated from the LSS data. The approach used is a conventional one

that finds a variance for the estimated LAR (on the log scale) induced by the variances of these three sources. The computational approach for the subjective confidence intervals is detailed in Annex 12-C. Additional sources of uncertainty that have not been quantified are discussed later in the chapter. For site-specific cancers other than leukemia, the assessment of sampling variability did not include uncertainty in the parameters quantifying the modifying effects of age at exposure and attained age. Although estimates of solid cancer risks are obtained as the sum of site-specific risks, uncertainty in these estimates was evaluated using models for all solid cancers.

RESULTS OF RISK CALCULATIONS

Lifetime risk estimates for the US population

In this section, the Committee's preferred estimates of the lifetime attributable risk (LAR) are presented for several cancer categories. Estimates of the numbers of excess cancers or deaths due to cancer in a population of 100,000 exposed to 0.1 Gy are emphasized, and are intended to apply to a population with an age composition similar to the 1999 US population. In addition, estimates for all solid cancers and for leukemia are presented for three specific exposure ages (10, 30, and 50 years), for a population that is exposed throughout life to one mGy per year, and a population that is exposed to 10 mGy per year from age 18 to 65. Additional examples are found in Annex 12 D.

For perspective, Table 12-4 shows lifetime risks of cancer incidence and mortality in the absence of exposure. For nearly all sites other than breast, ovary, and thyroid, risks are larger for males than females with especially large differences for cancers of the liver and bladder. In males, prostate cancer accounts for more than a third of the incident cases. In females, breast cancer accounts for about a third of the incident cases.

TABLE 12-4 Baseline lifetime risk estimates of cancer incidence and mortality. Number of estimated cancer cases or deaths in population of 100,000. (Number of years of life lost per death).

	Incidence		Mortality	
Cancer site	Males	Females	Males	Females
Solid cancer[a]	45,500	36,900	22,100 (11)	17,500 (11)
Stomach	1200	720	670 (11)	430 (12)
Colon	4200	4200	2200 (11)	2100 (11)
Liver	640	280	490 (13)	260 (12)
Lung	7700	5400	7700 (12)	4600 (14)
Breast	--	12,000	--	3000 (15)
Prostate	15,900	--	3500 (8)	--
Uterus	--	3000	--	750 (15)
Ovary	--	1500	--	980 (14)
Bladder	3400	1100	770 (9)	330 (10)
Other solid cancer	12,500	8800	6800 (13)	5100 (13)
Thyroid	230	550	40 (12)	60 (12)
Leukemia	830	590	710 (12.0)	530 (13)

[a]Solid cancer incidence estimates exclude thyroid and non-melanoma skin cancers.

TABLE 12-5a Lifetime attributable risk (LAR) of site-specific solid cancer incidence. Number of cases per 100,000 exposed persons of mixed ages exposed to 0.1 Gy.

	Males			Females		
Cancer Site	LAR based on relative risk transport[a]	LAR based on absolute risk transport[b]	Combined and adjusted by DDREF[c] (Subjective 95% CI[d])	LAR based on relative risk transport[a]	LAR based on absolute risk transport[b]	Combined and adjusted by DDREF[c] (Subjective 95% CI[d])
Incidence						
Stomach	25	280	34 (3, 350)	32	330	43 (5, 390)
Colon	260	180	160 (66, 360)	160	110	96 (34, 270)
Liver	23	150	27 (4, 180)	9	85	12 (1, 130)
Lung	250	190	140 (50, 380)	740	370	300 (120, 780)
Breast				510 Not used	460	310 (160, 610)
Prostate	190	6	44 (<0, 1860)			
Uterus				19	81	20 (<0, 131)
Ovary				66	47	40 (9, 170)
Bladder	160	120	98 (29, 330)	160	100	94 (30, 290)
Other	470	350	290 (120, 680)	490	320	290 (120, 680)
Thyroid	32	No model	21 (5, 90)	160	No model	100 (25, 440)
Sum of site-specific estimates	1400	1310[e]	800	2310[f]	2060[e]	1310
All solid cancer model[g]	1550	1250	970 (490, 1920)	2230	1880	1410 (740, 2690)

[a]Linear estimate based on ERR models shown in Table 12-2 with no DDREF adjustment
[b]Linear estimate based on EAR models shown in Table 12-2 with no DDREF adjustment.
[c]The estimates were obtained as a weighted average (on a logarithmic scale) of estimates based on relative and absolute risk transport. For sites other than lung, breast and thyroid, relative risk transport was given a weight of 0.7 and absolute risk transport was given a weight of 0.3. These weights were reversed for lung cancer. Models for breast and thyroid cancer were based on data that included Caucasian subjects. The resulting estimates were reduced by a dose and dose rate effectiveness factor (DDREF) of 1.5
[d]Including uncertainty from sampling variability, transport, and DDREF. Sampling uncertainty in the parameters that quantify the modifying effects of age at exposure and attained age is not included except for the all solid cancer model..
[e]Includes thyroid cancer estimate based on ERR model.
[f]Includes breast cancer estimate based on EAR model.
[g]Estimates based on model developed by analyzing LSS incidence data on all solid cancers excluding thyroid cancer and non-melanoma skin cancer as a single category. See Table 12-1.

TABLE 12-5b Lifetime attributable risk (LAR) of site-specific solid cancer mortality. Number of deaths per 100,000 exposed persons of mixed ages exposed to 0.1 Gy.

	Males			Females		
Cancer Site	LAR based on relative risk transport[a]	LAR based on absolute risk transport[b]	Combined and adjusted by DDREF[c] (Subjective 95% CI[d])	LAR based on relative risk transport[a]	LAR based on absolute risk transport[b]	Combined and adjusted by DDREF[c] (Subjective 95% CI[d])
Stomach	14	150	19 (2, 190)	19	190	25 (3, 220)
Colon	130	89	76 (32, 180)	78	50	46 (16, 130)
Liver	16	120	20 (3, 150)	8	84	11 (1, 130)
Lung	240	200	140 (52, 380)	620	340	270 (110, 660)
Breast				110 Not used	110	73 (37, 150)
Prostate	35	1	9 (<0, 300)			
Uterus				4	24	5 (<0, 38)
Ovary				37	34	24 (6, 98)
Bladder	34	31	22 (7, 73)	45	36	28 (10, 81)
Other	180	190	120 (54, 280)	200	180	132 (61, 280)
Sum of site-specific estimates	650	780	410	1120[e]	1050	610
All solid cancer model[f]	760	650	480 (240, 980)	1200	940	740 (370, 1500)

[a]Linear estimate based on ERR models shown in Table 12-2 with no DDREF adjustment
[b]Linear estimate based on EAR models shown in Table 12-2 with no DDREF adjustment.
[c]The estimates were obtained as a weighted average (on a logarithmic scale) of estimates based on relative and absolute risk transport. For sites other than lung, breast and thyroid, relative risk transport was given a weight of 0.7 and absolute risk transport was given a weight of 0.3. These weights were reversed for lung cancer. Models for breast and thyroid cancer were based on data that included Caucasian subjects. The resulting estimates were reduced by a dose and dose rate effectiveness factor (DDREF) of 1.5
[d]Including uncertainty from sampling variability, transport, and DDREF. Sampling uncertainty in the parameters that quantify the modifying effects of age at exposure and attained age is not included except for the all solid cancer model.
[e]Includes breast cancer estimate based on EAR model.
[f]Estimates based on model developed by analyzing LSS mortality data on all solid cancers as a single category. See Table 12-1.

Tables 12-5a and 12-5b show estimates of the LAR for a population with an age composition similar to that of the US population exposed to 0.1 Gy. Estimates of cancer incidence (12-5a) and mortality (12-5b) are shown for several site-specific solid cancers. The committee's preferred estimates are those in the third and sixth columns. These were obtained by calculating a weighted mean (on a logarithmic scale) of linear estimates based on relative and absolute risk transport (also shown) and then reducing them by a dose and dose rate reduction factor (DDREF) of 1.5 as described earlier. The subjective confidence intervals reflect uncertainty due to sampling variability, transport, and DDREF. For most sites, these intervals cover at least an order of magnitude. For many sites, statistical uncertainty alone is large (see Table 12-2). For cancers of the stomach, liver, lung (females), prostate, and uterus, estimates based on relative and absolute risk differ by a factor of two or more, contributing substantially to the uncertainty in estimates for these sites. It is perhaps surprising that the LAR for lung cancer is nearly twice as large for females as males even though the baseline risks show a reverse pattern. It is possible that this and other patterns for site-specific cancers reflect statistical anomalies or other biases in LARs estimated with high uncertainty.

The committee's preferred estimates for risk of all solid cancers can be obtained as the sums of the site-specific estimates, and are shown in the next to the last line of Tables 12-5a and 12-5b. These estimates are larger for females than males, even though the reverse is true for baseline risks (Table 12-4), a finding that comes about primarily because of the contribution of breast cancer and lung cancer (as noted above). For cancer mortality, the years of life lost per death is also of interest. For the sum of sites estimates, this was 14 per death for males and 15 per death for females

The LAR for all cancer incidence is about twice that for cancer mortality. However, this ratio varies greatly by cancer site. The largest contribution to cancer incidence in males is from the residual category of "other solid cancers" followed by colon and lung cancer. These three categories are also the most important contributors to cancer mortality. Cancers of the lung, breast, and other solid cancers contribute about equally to cancer incidence in females. Lung cancer is the most important contributor to cancer mortality in females.

Although the committee's preferred estimates for all solid cancers are the sums of the site-specific estimates, for comparison, the last line of Tables 12-5 shows estimates based on models developed by analyzing LSS data incidence and mortality data on all solid cancers as a single category (see Table 12-1). These estimates are generally about 20% higher than those obtained using the sum of sites approach, a difference that comes about in part because of the weighting scheme used to combine estimates based on relative and absolute risk transport (particularly the greater weight given to absolute risk transport for lung cancer), and because of the use of the model developed by Preston and others (2002a) for breast cancer, similar to assuming absolute risk transport for this site.

Table 12-6. Committee's preferred estimates of lifetime attributable risk (LAR) of solid cancer incidence and mortality[a] with 95% subjective confidence intervals[b]. Number of cases or deaths per 100,000 exposed persons.

	Incidence		Mortality	
	Males	Females	Males	Females
Exposure scenario				
0.1 Gy to population of mixed ages	800 (400, 1590)	1310 (690, 2490)	410 (200, 830)	610 (300, 1230)
0.1 Gy at age 10	1330 (660, 2660)	2530 (1290, 4930)	640 (300, 1390)	1050 (470, 2330)
0.1 Gy at age 30	600 (290, 1260)	1000 (500, 2020)	320 (150, 650)	490 (250, 950)
0.1 Gy at age 50	510 (240, 1100)	680 (350, 1320)	290 (140, 600)	420 (210, 810)
1 mGy per year throughout life	550 (280, 1100)	970 (510, 1840)	290 (140, 580)	460 (230, 920)
10 mGy per year from ages 18 to 65	2600 (1250, 5410)	4030 (2070, 7840)	1410 (700, 2860)	2170 (1130, 4200)

[a]These were obtained as the sum of site-specific LAR estimates. The site-specific estimates were obtained as a weighted average (on a logarithmic scale) of estimates based on relative and absolute risk transport. For sites other than lung, breast and thyroid, relative risk transport was given a weight of 0.7 and absolute risk transport was given a weight of 0.3. These weights were reversed for lung cancer. Models for breast and thyroid cancer were based on data that included Caucasian subjects. The resulting linear estimates were reduced by a dose and dose rate effectiveness factor (DDREF) of 1.5

[b]Including uncertainty from sampling variability, transport, and DDREF. The uncertainty evaluation was based on evaluation of estimates based on analyses of LSS cohort data on all solid cancers analyzed as a single category as described in Annex 12 C.

TABLE 12-7 Lifetime attributable risk (LAR) of leukemia incidence and mortality. Number of cases or deaths per 100,000 exposed persons.[a]

	Males			Females		
Exposure Scenario	LAR based on relative risk transport[b]	LAR based on absolute risk transport[c]	Committee's preferred estimate[d] (Subjective 95% CI[e])	LAR based on relative risk transport[b]	LAR based on absolute risk transport[c]	Committee's preferred estimate[d] (Subjective 95% CI[e])
Incidence						
0.1 Gy to population of mixed ages	120	64	100 (33, 300)	94	38	72 (21, 250)
0.1 Gy at age 10	140	85	120 (40, 360)	110	50	86 (25, 300)
0.1 Gy at age 30	87	77	84 (31, 230)	69	49	62 (22, 170)
0.1 Gy at age 50	110	45	84 (24, 290)	84	30	62 (16, 230)
1 mGy per year throughout life	83	40	67 (19, 230)	68	26	51 (13, 200)
10 mGy per year from ages 18 to 65	430	240	360 (110, 1140)	340	160	270 (79, 920)
Mortality						
0.1 Gy to population of mixed ages	88	40	69 (22, 220)	71	25	52 (14, 190)
0.1 Gy at age 10	88	42	70 (21, 240)	71	26	53 (13, 210)
0.1 Gy at age 30	70	53	64 (23, 180)	59	36	51 (17, 150)
0.1 Gy at age 50	93	37	71 (20, 250)	74	26	54 (14, 210)
1 mGy per year throughout life	62	25	47 (13, 180)	53	17	38 (9, 160)
10 mGy per year from ages 18 to 65	350	170	290 (84, 970)	290	120	220 (61, 820)

[a]All estimates are based on linear-quadratic model.
[b]Based on ERR model shown in Table 12-4.
[c]Based on EAR model shown in Table 12-4.
[d]Obtained as a weighted mean (on a logarithmic scale) with weights of 0.7 for the relative risk transport estimate and a weight of 0.3 for the absolute risk transport estimate.
[e]Including uncertainty from sampling variability and transport. Sampling uncertainty includes uncertainty in both the linear and quadratic terms of the dose-response.

Table 12-6 shows estimates of the all solid cancer LARs for several exposure scenarios. In each case, these were obtained as the sum of the site-specific estimates. Additional detail is shown in Annex 12-D. Because models for most cancers allow for a decrease in both the ERR and EAR with increasing age at exposure, estimates for persons exposed at age 10 are more than twice those for persons exposed at ages 30 or 50. However, because models allow for no further decrease after age 30, the difference in lifetime risk estimates for persons exposed at ages 30 and 50 are not as great. Also shown are estimates of the LAR for chronic lifetime exposure to one mGy per year and of the LAR for an occupational scenario of exposure to 10 mGy per year from ages 18 to 65.

Table 12-7 shows estimates of the LARs for leukemia incidence and mortality for several exposure scenarios. The number of years of life lost per death was estimated to be 20 years for males and 21 years for females, values that are larger than those for solid cancers. Although the transport model has not been considered to be a major source of uncertainty in leukemia risk estimates (UNSCEAR 2000b; NIH 2003), Table 12-7 shows that LAR estimates based on relative risk transport are larger than those based on absolute risk transport, with the ratio ranging from about one to three. This is not due to the contribution of chronic lymphatic leukemia (CLL) since CLL was excluded from the baseline rates used to calculate LARs based on relative risk transport. The Committee's preferred estimates are based on a weighted mean of LAR estimates obtained from the two transport models as with most site-specific solid cancers, and the subjective confidence intervals include transport uncertainty. Unlike solid cancer models, the leukemia models (Table 12-3) are based on linear-quadratic functions of dose, so there is no need for further reduction by a DDREF. Uncertainty calculations include sampling uncertainty in both the linear coefficient and the curvature parameter. Previous risk assessments have considered leukemia incidence and mortality to be very similar, and this was likely the case in the time period when much of the LSS leukemia data was obtained. However, currently leukemia is not always rapidly fatal, and we have thus reduced estimates based on the LSS cohort for estimating leukemia mortality (see section on "Methods of calculating lifetime risks"). For a single exposure of 0.1 Gy to a population of mixed ages, leukemia mortality estimates are about 30% lower than those for leukemia incidence.

Detailed tables showing lifetime risk estimates are found in Annex 12 D. Annex 12 D also gives examples of use of these tables to obtain risk estimates for specific exposure scenarios.

Comparison of BEIR VII Risk Estimates with Those from Other Sources

Tables 12-8 and 12-9 compare the BEIR VII Committee's lifetime risk estimates with estimates recommended by other organizations in recent years. A description of the approaches used to obtain these earlier risk estimates is given in Annex 12-A. The ICRP and EPA solid cancer estimates include reduction by a DDREF of 2 (except for the EPA estimates for breast and thyroid cancers where linear estimates were used without reduction). Neither BEIR V nor UNSCEAR made specific recommendations regarding reduction of risks at low dose and dose rates. Estimates from these organizations are shown both with no reduction, and, to facilitate comparison with BEIR VII estimates, reduced by a DDREF of 1.5 with the latter shown in parentheses. UNSCEAR presents estimates for site-specific solid cancers based on both relative and absolute risk transport models without expressing a preference. Again to facilitate comparison, the UNSCEAR estimates in parentheses combine these estimates using the same approach adopted by the BEIR VII committee and reducing them by a DDREF of 1.5.

BEIR VII, BEIR V (1990), and UNSCEAR (2000b) present estimates that are sex-specific, whereas ICRP (1991) and EPA (1999) present a single estimate for both sexes. Table 12-8 addresses comparisons that include cancer mortality estimates developed by the ICRP and EPA. Thus, the estimates in this table from BEIR V, UNSCEAR 2000, and BEIR VII are averages of estimates for males and females. The BEIR V leukemia estimates

ANNEX 12 D. ADDITIONAL EXAMPLES OF LIFETIME RISK ESTIMATES BASED ON BEIR VII PREFERRED MODELS.

Tables 12 D-1 and 12 D-2 show lifetime risk estimates for cancer incidence and mortality resulting from a single dose of 0.1 Gy at several specific ages. Estimates are shown for all cancer, leukemia, all solid cancer, and for cancer of several specific sites. Table 12D-3 shows analogous lifetime risk estimates for exposure to one mGy per year throughout life and to 10 mGy per year from ages 18 to 65. The examples below illustrate how these tables may be used to obtain estimates for other exposure scenarios. For clarity of presentation, we have generally shown more decimal places than are justified .

Example 1: A 10-year old male receives a dose of 0.01 Gy (10 mGy) to the colon from a CT scan. Table 12 D-1 shows the estimated lifetime risk of being diagnosed with colon cancer for a male exposed to 0.1 Gy at age 10 as 241 per 100,000. The estimate for a male exposed at 0.01 Gy is obtained as (0.01/0.1) x 241 = 24.1 per 100,000 (about 1 in 4000). An estimate of the lifetime risk of dying of colon cancer can also be obtained using Table 12 D-2, and is (0.01/0.1) x 117 = 11.7 per 100,000 (about 1 in 8500).

Example 2: A 45-year old woman receives a dose of 0.001 Gy (1 mGy) to the breast from a mammogram.. Table 12 D-1 shows an estimated lifetime risk of being diagnosed with breast cancer for a female exposed to 0.1 Gy at age 40 as 141 per 100,000; the comparable estimate for exposure at age 50 is 70 per 100,000. Using linear interpolation, the risk from exposure to 0.1 Gy at age 45 is (141 + 70)/2 =105.5 per 100,000. The risk from exposure to 0.001 Gy is estimated as (0.001/0.1) x 105.5 = 1.055 per 100,000. A rough estimate of the risk from repeated annual mammograms could be obtained by adding estimates obtained from receiving a mammogram at ages 45, 46, 47, 48, etc. For most purposes, such an estimate will be reasonable although this approach does not account for the possibility of dying before subsequent doses are received.

Example 3: A female is exposed to high natural background of 0.004 Gy (4 mGy) per year throughout life. Lifetime risk estimates for exposure to 0.001 Gy (1 mGy) per year throughout life are shown in columns 2 (incidence) and 4 (mortality) of Table 12 D-3. To obtain estimates for exposure to 4 mGy throughout life, these estimates must be multiplied by 4. For example, the estimated risk of a female being diagnosed with a solid cancer would be 3872 per 100,000 (4 x 968) whereas the risk of being diagnosed with leukemia would be 204 (4 x 51) per 100,000 yielding a total risk of being diagnosed with cancer 4076 per 100,000 (about 1 in 25). The risk of dying of cancer can be obtained in a similar manner and would be 1988 per 100,000 (about 1 in 50).

TABLE 12 D-1 Lifetime attributable risk (LAR) of site-specific solid cancer incidence. Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy.

Cancer Site	Age at exposure (years)										
	0	5	10	15	20	30	40	50	60	70	80
Males											
Stomach	76	65	55	46	40	28	27	25	20	14	7
Colon	336	285	241	204	173	125	122	113	94	65	30
Liver	61	50	43	36	30	22	21	19	14	8	3
Lung	314	261	216	180	149	105	104	101	89	65	34
Prostate	93	80	67	57	48	35	35	33	26	14	5
Bladder	209	177	150	127	108	79	79	76	66	47	23
Other	1123	672	503	394	312	198	172	140	98	57	23
Thyroid	115	76	50	33	21	9	3	1	0.3	0.1	0.0
All solid	2326	1667	1325	1076	881	602	564	507	407	270	126
Leukemia	237	149	120	105	96	84	84	84	82	73	48
All cancers	2563	1816	1445	1182	977	686	648	591	489	343	174
Females											
Stomach	101	85	72	61	52	36	35	32	27	19	11
Colon	220	187	158	134	114	82	79	73	62	45	23
Liver	28	23	20	16	14	10	10	9	7	5	2
Lung	733	608	504	417	346	242	240	230	201	147	77
Breast	1171	914	712	553	429	253	141	70	31	12	4
Uterus	50	42	36	30	26	18	16	13	9	5	2
Ovary	104	87	73	60	50	34	31	25	18	11	5
Bladder	212	180	152	129	109	79	78	74	64	47	24
Other	1339	719	523	409	323	207	181	148	109	68	30
Thyroid	634	419	275	178	113	41	14	4	1	0.3	0.0
All solid	4592	3265	2525	1988	1575	1002	824	678	529	358	177
Leukemia	185	112	86	76	71	63	62	62	57	51	37
All cancers	4777	3377	2611	2064	1646	1065	886	740	586	409	214

[a]These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a dose and dose rate effectiveness factor (DDREF) of 1.5, except for leukemia, which is based on a linear-quadratic model.

TABLE 12 D-2. Lifetime attributable risk (LAR) of site-specific solid cancer mortality. Number of deaths per100,000 persons exposed to a single dose of 0.1 Gy at age 10, 30 and 50 years.[a]

Cancer Site	Age at exposure (years)										
	0	5	10	15	20	30	40	50	60	70	80
Males											
Stomach	41	34	30	25	21	16	15	13	11	8	4
Colon	163	139	117	99	84	61	60	57	49	36	21
Liver	44	37	31	27	23	16	16	14	12	8	4
Lung	318	264	219	182	151	107	107	104	93	71	42
Prostate	17	15	12	10	9	7	6	7	7	7	5
Bladder	45	38	32	27	23	17	17	17	17	15	10
Other	400	255	200	162	134	94	88	77	58	36	17
All solid	1028	781	641	533	444	317	310	289	246	181	102
Leukemia	71	71	71	70	67	64	67	71	73	69	51
All cancers	1099	852	712	603	511	381	377	360	319	250	153
Females											
Stomach	57	48	41	34	29	21	20	19	16	13	8
Colon	102	86	73	62	53	38	37	35	31	25	15
Liver	24	20	17	14	12	9	8	8	7	5	3
Lung	643	534	442	367	305	213	212	204	183	140	81
Breast	274	214	167	130	101	61	35	19	9	5	2
Uterus	11	10	8	7	6	4	4	3	3	2	1
Ovary	55	47	39	34	28	20	20	18	15	10	5
Bladder	59	51	43	36	31	23	23	22	22	19	13
Other	491	287	220	179	147	103	97	86	69	47	24
All solid	1717	1295	1051	862	711	491	455	415	354	265	152
Leukemia	53	52	53	52	51	51	52	54	55	52	38
All cancers	1770	1347	1104	914	762	542	507	469	409	317	190

[a]These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a dose and dose rate effectiveness factor (DDREF) of 1.5 except for leukemia, which is based on a linear-quadratic model.

TABLE 12 D-3 Lifetime attributable risk (LAR) of site-specific solid cancer incidence and mortality. Number of cases or deaths per 100,000 persons exposed to 1 mGy per year throughout life or to 10 mGy per year from ages 18 to 64.[a]

	Incidence		Mortality	
	Exposure scenario		Exposure scenario	
Cancer site	1 mGy per year throughout life	10 mGy per year from ages 18 to 65	1 mGy per year throughout life	10 mGy per year from ages 18 to 65
Males				
Stomach	24	123	13	66
Colon	107	551	53	273
Liver	18	93	14	72
Lung	96	581	99	492
Prostate	32	164	6.3	32
Bladder	69	358	16	80
Other	194	801	85	395
Thyroid	14	28		
All solid	554	2699	285	1410
Leukemia	67	360	47	290
All cancers	621	3059	332	1700
Females				
Stomach	32	163	19	94
Colon	72	368	34	174
Liver	8.7	44	8	40
Lung	229	1131	204	1002
Breast	223	795	53	193
Uterus	14	19	3.5	18
Ovary	29	140	18	91
Bladder	71	364	21	108
Other	213	861	98	449
Thyroid	75	139		
All solid	968	4025	459	2169
Leukemia	51	270	38	220
All cancers	1019	4295	497	2389

[a]These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a dose and dose rate effectiveness factor (DDREF) of 1.5 except for leukemia, which is based on a liner-quadratic model.

a

duplications of genomic segments) with a resolution beyond the level of a light microscope.

EPIDEMIOLOGIC STUDIES OF POPULATIONS EXPOSED TO IONIZING RADIATION

A-bomb survivor studies

The Life Span Study (LSS) cohort of survivors of the atomic bombings in Hiroshima and Nagasaki continues to serve as a major source of information for evaluating health risks from exposure to ionizing radiation, and particularly for developing quantitative estimates of risk. Its advantages include its large size, the inclusion of both sexes and all ages, a wide range of doses that have been estimated for individual subjects, and high quality mortality and cancer incidence data. In addition, the whole body exposure received by this cohort offers the opportunity to assess risks for cancers of a large number of specific sites and to evaluate the comparability of site-specific risks.

As an illustration, Figure 13-1 shows estimated excess relative risks of solid cancer versus dose (averaged over sex, and standardized to represent individuals exposed at age 30 and at attained age 60), for atomic bomb survivors with doses in each of 11 dose intervals less than 2.0 Sv. This plot helps convey the overall dose-response relationship from the LSS cohort and its role in low-dose risk estimation. Specific models are detailed in Chapter 6. It is important to note that the difference between the linear and linear-quadratic models in the low-dose ranges is small relative to the error bars; therefore, the difference between these models is small relative to the uncertainty in the risk estimates produced from them. For solid cancer incidence the linear-quadratic model did not offer statistically significant improvement in the fit, so the linear model was used. For leukemia, a linear-quadratic model (insert figure 13-1) was used since it fitted the data significantly better than the linear model.

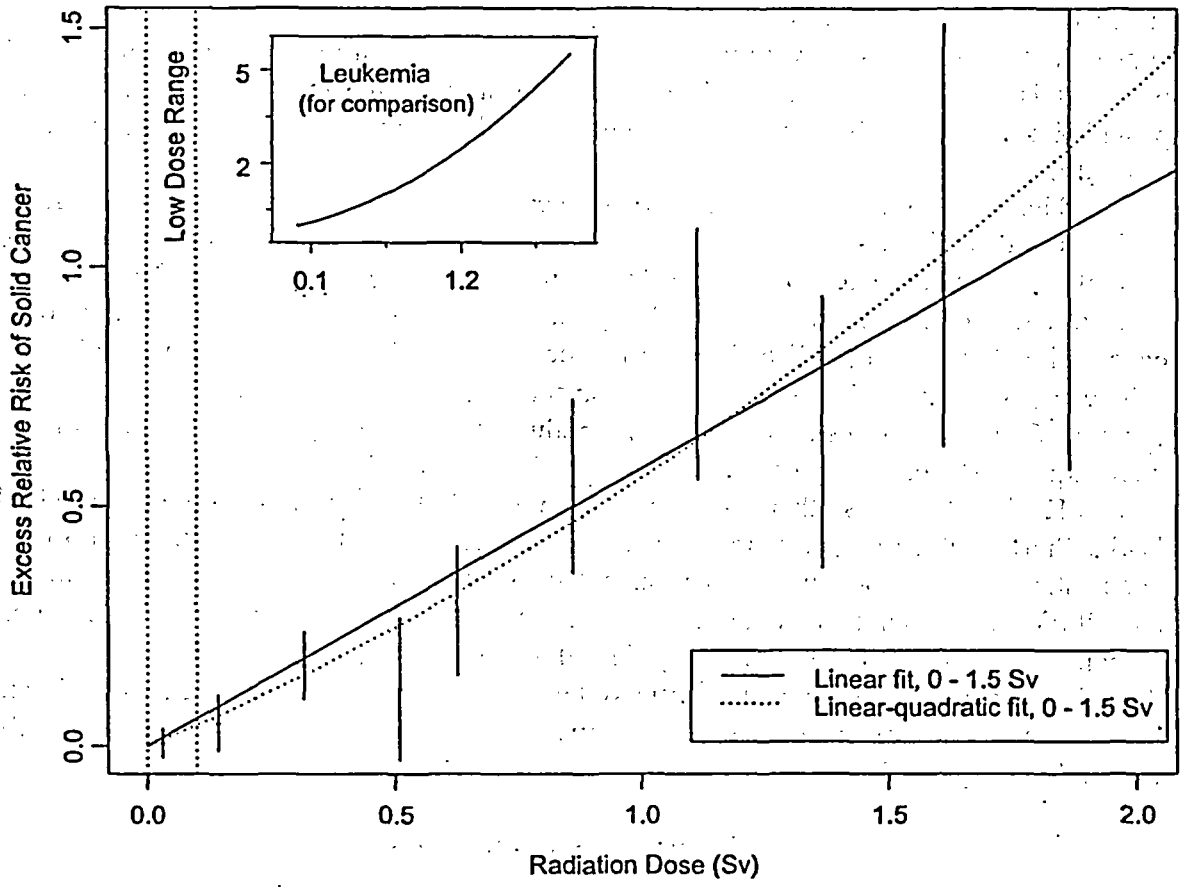

FIGURE 13-1. Excess Relative Risks of Solid Cancer for the Japanese Atomic Bomb Survivors. The plotted points are the estimated excess relative risks of solid cancer incidence (averaged over sex, and standardized to represent individuals exposed at age 30 and at attained age 60) for atomic bomb survivors with doses in each of 10 dose intervals, plotted above the midpoints of the dose intervals. If R(*d*) represents the age-specific instantaneous risk at some dose *d*, then the *excess relative risk* at dose *d* is [R(*d*) – R(0)]/R(0) (which is necessarily zero when dose is zero). The vertical lines are approximate 95% confidence intervals. The solid and dotted lines are estimated linear and linear-quadratic models for excess relative risk, estimated from all subjects with doses in the range 0 to 1.5 Sv. (These are not estimated from the points; but from the lifetimes and doses of the individual survivors, using statistical methods discussed in Chapter 6). A linear-quadratic model will always fit the data better than a linear model, since the linear model is a restricted special case with quadratic coefficient equal to zero. For solid cancer incidence, however, there is no *statistically significant* improvement in fit due to the quadratic term. It should also be noted that in the low dose range of interest the difference between the estimated linear and linear-quadratic models is small relative to the 95% confidence intervals. The insert shows the fit of a linear-quadratic model for leukemia, to illustrate the greater degree of curvature observed for that cancer.

The full LSS cohort consists of approximately 120,000 persons who were identified at the time of the 1950 census. However, most recent analyses have been restricted to approximately 87,000 survivors who were in the city at the time of the bombings and for whom it is possible to estimate doses. Special studies of subgroups of the LSS have provided clinical data, biological measurements, and information on potential confounders or modifiers.

The availability of high quality cancer incidence data has resulted in several analyses and publications addressing specific cancer sites. These analyses often include special pathological review of the cases and sometimes include data on additional variables (such as smoking for the evaluation of lung cancer risks). Papers focusing on the following cancer sites have been published in the last decade: female breast cancer, thyroid cancer, salivary gland cancer, liver cancer, lung cancer, skin cancer and central nervous system tumors. Special analyses have also been conducted of cancer mortality in survivors who were exposed either *in utero* or during the first five years of life.

Health endpoints other than cancer have been linked with radiation exposure in the LSS cohort. Of particular note, a dose-response relationship with mortality from non-neoplastic disease mortality was demonstrated in 1992, and subsequent analyses in 1999 and 2003 have strengthened the evidence for this association. Statistically significant associations were seen for the categories of heart disease, stroke, and diseases of the digestive, respiratory and hematopoietic systems. The data were inadequate to distinguish between a linear dose-response, a pure quadratic response or a dose-response with a threshold as high as 0.5 Sv.

Medical radiation studies

The published studies on health effects of medical exposures were reviewed to identify those that provide information for quantitative risk estimation. Particular attention was focused on estimating risks of leukemia and of lung, breast, thyroid and stomach cancer in relation to radiation dose for comparison with the estimates derived from other exposed populations, in particular the atomic bomb survivors. The possible association between radiation exposure and cardiovascular mortality and morbidity was also reviewed.

For lung cancer, the ERR per Gy from the studies of acute high dose-rate exposures are statistically compatible and in the range 0.1-0.4 per Gy. It is difficult to evaluate the effects of age at exposure or of exposure protraction based on these studies as only one study (that of the hemangioma cohort) is available in which exposure occurred at very young ages and in which protracted low dose-rate exposures were received. The study of tuberculosis patients, however, appears to indicate that substantial fractionation of exposure leads to a reduction of risk.

For breast cancer, EARs appear to be similar - of the order of 9.9 per 10^4 PY per Gy at age 50 - following acute and fractionated moderate to high dose-rate exposure. Effects of attained age and age at exposure are important modifiers of risk. The excess risks appear to be higher in populations of women treated for benign breast conditions, suggesting that these women may be at an elevated risk of radiation induced breast cancer. The hemangioma cohorts showed lower risks, suggesting a possible reduction of risks following protracted low dose-rate exposures.

APPENDIX C

ISSUES RAISED BY THE INSTITUTE FOR ENERGY AND ENVIRONMENT RESEARCH (IEER)

A letter dated September 3, 1999 and authored by Ms. Lisa Ledwidge and Dr. Arjun Makhijani on behalf of IEER and a number of other signatories requested that the BEIR VII committee address six issues. Our response to these issues follows.

1. Effects of radionuclides that cross the placenta

In Chapter 8 the Committee considers post-Chernobyl data on the excess papillary thyroid cancers arising in radio-iodine exposed children, some of whom received their exposure *in utero*. With respect to carbon-14 and tritium, brief comments are made in response to issue 3. We recommend that this issue be addressed as part of a larger review of maternal exposures in humans that may affect the fetus.

2. Effects of radiation on female fetuses

In Chapters 6 and 7, the committee considers the effects of *in utero* radiation, including medical radiation and radiation from the atomic bombs. In the recent paper by Delongchamp (Delongchamp and others 1997), nine cancer deaths among females exposed *in utero* to the atomic bombs were noted in comparison to only one among males. Minimal information exists in the medical literature with respect to sex-specific effects, and none report a gender-specific association between radiation and cancer. Because of the current practice of minimizing radiation exposure to pregnant women, the committee considers it unlikely that this issue will be able to be addressed by future epidemiologic studies.

3. Effects of organically-bound radionuclides

Cellular and animal data are available for the development of judgments on the tumorigenic, genetic, developmental effects of tritiated water and organically-bound tritium (Straume 1991; Straume and Carsten 1993). The tritium effects observed do not differ qualitatively from those resulting from external irradiation with x rays or gamma rays. The evidence available indicates that the relative biological effectiveness (RBE) of beta-irradiation from tritium is generally greater (2-3 fold) than that of gamma-irradiation and similar to or slightly greater (1-2 fold) than x-irradiation. Higher effectiveness is seen in *in vitro* cellular studies when tritium is incorporated into DNA (*e.g.* as tritiated thymidine). Although the observed effects of tritium are largely attributable to ionization damage from beta-particles, transmutation of incorporated tritium to helium also has the potential to damage DNA (NCRP 1979; Hill and Johnson 1993) (NCRP 1979; Hill and Johnson 1993). However, following ingestion of organically-bound tritium (OBT - including tritiated thymidine) the *in vivo* activity of digestive metabolic processes means that only a very

small fraction of tritium is incorporated into cellular DNA. Thus the predominant *in vivo* source of DNA damage from OBT is beta-particle ionization, not transmutation. The observed *in vivo* effects of tritium will, in any event, include any contribution from transmutational damage to DNA. The same general principles also apply to *in vivo* effects from organically-bound carbon-14.

It is important to point out that the Committee was not constituted to review the biokinetic aspects of doses from internal radionuclides such as tritium, carbon-14, strontrium-90, radio-cesium and radioiodine. Nevertheless the BEIR VII committee considered potentially informative epidemiologic data that relate to risks from internal radiation as part of their brief to review risks at low doses of low LET radiation.

4. Synergistic effects

This issue has been comprehensively addressed in the Annex H of the UNSCEAR Report (UNSCEAR 2000b). The BEIR committee endorses the recommendations made on page 217 of that report.

5. Data integrity and quality

We have addressed this issue in chapter 8 on Occupational Radiation Studies. The Committee acknowledges that there is imprecision in exposure estimates of all epidemiologic studies, especially in retrospective studies of occupational groups. In general, however, studies of workers exposed to radiation tend to have better exposure data than that in studies of workers exposed to chemicals because of the concurrent estimation of exposure through use of radiation badges.

The committee notes that imprecision in estimation of radiation exposure will tend toward an under-estimation of any true association between radiation and health effects. To the extent that models based on these data are utilized to set standards of population exposure, the standards will tend to be lower that those that would be based on completely accurate data.

6. Effects on various populations

The atomic bomb data are based on two populations in Japan at one point of time. The relation radiation exposure to age at exposure and gender have been extensively studied and are summarized in chapter 6. Data on occupational and medical exposure to radiation are available for a number of populations throughout the world and for many decades. However, few details are presented in these studies on age at exposure and sex, except, of course, for sex-specific studies.

The Committee recommends that future studies of populations exposed to ionizing radiation include not only information on factors that may interact with radiation exposure, but also information on possible risks present in persons with varying demographic characteristics.