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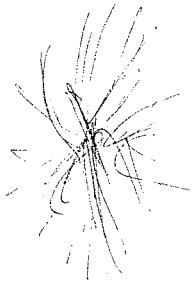
Health Effects Model for Nuclear Power Plant Accident Consequence Analysis

I: Introduction, Integration, and Summary

II: Scientific Basis for Health Effects Models



Principal Investigators:

September 1, 1983 to April 1, 1985 John S. Evans and Dade W. Moeller
July 1, 1982 to August 31, 1983 Douglas W. Cooper

Harvard School of Public Health
Boston, MA 02115 (9957)

Sandia Project Officer: Daniel J. Alpert
NRC Technical Project Monitor: James A. Martin

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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

JUL 16 1985

MEMORANDUM FOR: Recipients of NUREG/CR-4214

SUBJECT: REQUEST FOR COMMENT

NUREG/CR-4214, "Health Effects Model for Nuclear Power Plant Accident Consequence Analysis," was prepared for the Nuclear Regulatory Commission by the Harvard School of Public Health under subcontract to the Sandia National Laboratories.

It is anticipated that the methods and data set forth in this report will be used by the NRC in areas of broad public interest such as probabilistic risk analyses, emergency response planning, siting, NRR safety goal applications, and cost/risk/benefit analyses--indeed, wherever risks to public health need to be considered in regulatory applications. Thus, although a substantial peer review was conducted during the course of the study that resulted in the report, it is considered imperative that an opportunity for public comment on the results as presented in the report be provided. Comments should be sent to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: James A. Martin, Division of Risk Analysis and Operations. These comments will be most useful to the staff if they are received by November 1, 1985.

The NRC hereby expresses its great appreciation to all participants in this study for their considerable efforts, as well as to all who will take the time and effort to provide it with comments on this report.

Sincerely,

Frank P. Gillespie, Director
Division of Risk Analysis and
Operations
Office of Nuclear Regulatory Research

ABSTRACT

Analysis of the radiological health effects of nuclear power plant accidents requires models for predicting early health effects, cancers and benign thyroid nodules, and genetic effects. Since the publication of the Reactor Safety Study, additional information on radiological health effects has become available. This report summarizes the efforts of a program designed to provide revised health effects models for nuclear power plant accident consequence modelling.

The new models for early effects address four causes of mortality and nine categories of morbidity. The models for early effects are based upon two parameter Weibull functions. They permit evaluation of the influence of dose protraction and address the issue of variation in radiosensitivity among the population.

The piecewise-linear dose-response models used in the Reactor Safety Study to predict cancers and thyroid nodules have been replaced by linear and linear-quadratic models. The new models reflect the most recently reported results of the follow-up of the survivors of the bombings at Hiroshima and Nagasaki and permit analysis of both morbidity and mortality.

The new models for genetic effects allow prediction of genetic risks in each of the first five generations after an accident and include information on the relative severity of various classes of genetic effects.

The uncertainty in modelling radiological health risks is addressed by providing central, upper, and lower estimates of risks. An approach is outlined for summarizing the health consequences of nuclear power plant accidents.

PREFACE

This report is intended to provide the technical information required to develop improved radiological health consequence computer codes. It is not intended for general audiences and should not be considered an update of the BEIR III Report (1980). Much of the background information on the biological basis of radiation-induced health effects has not been included.

The report covers only dose-response relationships. It does not include information on releases, transport of radionuclides, or dosimetry. Therefore, it should not be construed as an update of Chapter 13 of Appendix VI of the Reactor Safety Study (1975).

The members of the Advisory Group and the external reviewing scientists have provided recommendations and criticisms but do not necessarily either individually or collectively endorse the revised models.

CONTRIBUTING SCIENTISTS

Volume I

Integration and Summary	John S. Evans, Sc.D. Harvard School of Public Health
	Dade W. Moeller, Ph.D. Harvard School of Public Health

Volume II

Chapter 1 *Early Occurring and Continuing Effects*	Fletcher Hahn, D.V.M., Ph.D. Lovelace Inhalation Toxicology Research Institute
	Bobby R. Scott, Ph.D. Lovelace Inhalation Toxicology Research Institute
Chapter 2 *Late Somatic Effects*	Ethel S. Gilbert, Ph.D. Battelle Pacific Northwest Laboratories
Chapter 3 *Genetic Effects*	Seymour Abrahamson, Ph.D. University of Wisconsin
	Michael A. Bender, Ph.D. Brookhaven National Laboratory
	Carter Denniston, Ph.D. University of Wisconsin
	William J. Schull, Ph.D. University of Texas
Appendix A *Thyroid Effects*	Harry Maxon, M.D. University of Cincinnati
	Steven A. Book, Ph.D. University of California
	C. Ralph Buncher, Sc.D. University of Cincinnati
	Vicki Hertzberg, Ph.D. University of Cincinnati
	Stephen R. Thomas, Ph.D. University of Cincinnati

REVIEWING SCIENTISTS

Volume I

Integration and Summary	Thomas B. Cochran, Ph.D. Natural Resources Defense Council
	Warren K. Sinclair, Ph.D. National Council on Radiation Protection and Measurements

Volume II

Chapter 1 *Early Occurring and Continuing Effects*	Troyce D. Jones, Ph.D. Oak Ridge National Laboratory
	Clarence C. Lushbaugh, M.D. Oak Ridge National Laboratory
Chapter 2 *Late Somatic Effects*	Roy E. Shore, Ph.D. New York University
Chapter 3 *Genetic Effects*	James F. Crow, Ph.D. University of Wisconsin
Appendix A *Thyroid Effects*	George B. Hutchison, M.D., M.P.H. Harvard School of Public Health
	Nan M. Laird, Ph.D. Harvard School of Public Health

MEMBERS OF ADVISORY GROUP

Seymour Abrahamson, Ph.D.
University of Wisconsin

William J. Bair, Ph.D.
Battelle Pacific Northwest Laboratories

Michael A. Bender, Ph.D.
Brookhaven National Laboratory

Victor P. Bond, M.D., Ph.D.
Brookhaven National Laboratory

Richard C. Cuddihy, Ph.D.
Lovelace Inhalation Toxicology Research Institute

Keith Eckerman, Ph.D.
Oak Ridge National Laboratory

Jacob I. Fabrikant, M.D., Ph.D.
University of California and
Lawrence Berkeley National Laboratory

Marvin Goldman, Ph.D.
University of California

George B. Hutchinson, M.D., M.P.H.
Harvard School of Public Health

Dade W. Moeller, Ph.D.
Harvard School of Public Health

Edward P. Radford, M.D.
Radiation Effects Research Foundation

Eugene L. Saenger, M.D.
University of Cincinnati College of Medicine

Warren K. Sinclair, Ph.D.
National Council on Radiation Protection and Measurements

Niel Wald, M.D.
University of Pittsburgh

Edward W. Webster, Ph.D.
Massachusetts General Hospital

Shlomo Yaniv, Ph.D.
U.S. Nuclear Regulatory Commission

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In addition, we owe a great debt to Cathy Crompton, Virgi Hepner, Diane McHenry, Avis Stiller, and Rita Zusman. Without their technical, clerical, and artistic contributions the report would not have been possible. A special thank you is extended to Dr. Richard Letz for his many contributions in mathematical modelling and computer programming, and to Susan LeVan for helping us when we needed it most.

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Chapter 1

INTRODUCTION

1.1 History and Goals

For several decades there has been interest in predicting the health effects of potential accidental releases of radionuclides from nuclear power plants. In 1975 the U.S. Nuclear Regulatory Commission (NRC) issued the Reactor Safety Study, which gave quantitative estimates of the health and economic consequences of such accidents. The health effects models (HEM) developed for the Reactor Safety Study have provided the basis for most of the official estimates made in recent years of the health consequences of nuclear power plant accidents. These models are used in several health consequence computer codes, e.g., CRAC, CRAC2, CRACIT.

In 1981 the NRC, through a contract with Sandia National Laboratories, began a critical review of the Reactor Safety Study HEM. This review, which was to "identify ranges of relative confidence and uncertainty, estimate degrees of conservatism, and identify areas in which there have been important research developments since formulation of the Reactor Safety Study model," was completed in late 1982, and the written summary report was issued in March 1983 (NRC, 1983).

In the Fall of 1982 the NRC initiated an effort to "prepare an improved health effects model to replace that presented in the Reactor Safety Study, paying particular attention to answering the needs indicated by" the critical reviewers. The results of that effort are presented in this report.

1.2 Process

Often the *process* used in the development of models, especially in controversial areas, has a significant impact on the results. The process followed in the development of the improved health effects models was largely determined by Sandia Laboratories and the Nuclear Regulatory Commission in conjunction with the original principal investigator, Dr. D.W. Cooper.

In the Fall of 1982 an Advisory Group consisting of fifteen experts was assembled. The Advisory Group was responsible for assisting in the selection of Working Groups and for reviewing the models developed by and the reports prepared by the Working Groups. Nominations for appointment to the Advisory Group had been solicited from over three hundred scientists, including: members of the National Academy of Science BEIR III Committee; members of the editorial boards of *Health Physics, Radiation Research, Journal of Nuclear Medicine, Medical Physics*, and the *International Journal of Radiation Biology*; officers of the Health Physics Society, American Board of Health Physics, and Radiation Research Society; members of the National Council on Radiation Protection and Measurements; award winners in Health Physics; members of the Medical Internal Radiation Dose Committee; members of the Power Reactor Health Physics Board of Examiners; and members of relevant divisions of the American National Standards Institute Main Committee. The names of the members of the Advisory Group and their affiliations are listed at the front of this volume.

At its first meeting, September 14, 1982, the Advisory Group made recommendations concerning the membership of the Working Groups. Largely on the basis of these recommendations, the Working Groups were assembled. The names of the people selected to serve as members of the Working Groups are listed at the front of this volume. The Working Groups were responsible for conducting literature reviews, making recommendations for health effects models, and for preparing reports summarizing the scientific basis for each recommended

model. Working Group Chairmen were advised to rely, where possible, on material that appeared in peer-reviewed (refereed) literature before June 30, 1983. Information from other sources was used in some cases, but only with the consent of the Principal Investigators and the Advisory Group.

In the Summer of 1983, the first draft of the report was completed. It was reviewed at a meeting of the Working Group Chairmen on August 29, 1983 and, after minor revisions, at a joint meeting of the Advisory and Working Groups on January 26 and 27, 1984.

In the Summer of 1984, the second draft of the report was completed. It was reviewed by the Advisory Group, the Working Groups, Sandia National Laboratories, the U.S. Nuclear Regulatory Commission, and a small group of "external" reviewers.

The final report was prepared the following winter and was released for publication late in the Spring of 1985.

1.3 Overview

The improved health effects model is in reality a collection of models. The collection is organized by class of effect (i.e., early effects, cancers, genetic effects) and by severity of effect (i.e., morbidity, mortality). Within these classes there are separate models for each of several effects of interest. For example, there are models for five different types of genetic effects (single gene dominant, single gene X-linked, chromosomal numerical aberrations [aneuploidy], chromosomal structural anomalies [unbalanced translocations], and multifactorial diseases), and for eight different types of cancer (leukemia, bone, breast, lung, gastrointestinal, thyroid, skin, and other). Table 1.1 lists the effects that are considered.

The health effects model represents one of many components within the family of nuclear power plant accidental consequence models. Other models are used to estimate the release and transport of contaminants, the evacuation and interdiction of populations, and the doses received. The *Overview of the Reactor Safety Study Consequence Models* (USNRC, 1977) provides a clear introduction to consequence modelling. The output from the release, transport, and dosimetry models is a set of estimates of organ-specific doses expected to be received by the population in each of several geographic cells surrounding a nuclear power plant as a function of time since an accident.

This set of organ-specific absorbed doses is the input required by our health effects model. The organ for which the absorbed dose is required for each effect is shown in Table 1.1. For some effects the dose rate is important as well as the dose. In these cases the dose received within each of several time intervals must be specified. Throughout the report, absorbed dose will be described simply as dose and will be stated in Gray (Gy).

The output from the models varies depending upon the effect of interest. For early and continuing effects, the risk is expressed as the probability that an individual will die from (or experience) the stated effect. These quantities are dimensionless. For late somatic effects, risks are typically expressed as the probabilities of dying from (or developing) the stated effect *within each of several time periods* after receiving a dose. These quantities are rates, with dimensions of probability per unit time, e.g., (yr^{-1}). By integrating somatic risks over an individual's lifetime, it is possible to obtain the lifetime risk of dying from (or developing) the stated effect. This is a probability, and is dimensionless. For genetic effects, risks are typically expressed as the probability that a child born a specified number of generations after a

Table 1.1 Effects for Which Quantitative Risk Estimation Models Have Been Developed

Index (i)	Effect	Model Developed For: Mortality	Model Developed For: Morbidity	Organ-Specific Dose
	Early and Continuing Effects			
1	hematopoietic syndrome	X	-[a]	bone marrow
2	pulmonary syndrome	X	-	lung
3	gastrointestinal syndrome	X	-	small intestine[b]/ colon
4	prenatal/neonatal deaths	X	-	fetus[c]
5	prodromal symptoms	-	X[a]	abdomen[d]
6	lung function impairment	-	X	lung
7	hypothyroidism[e]	-	X	thyroid
8	acute radiation thyroiditis	-	X	thyroid
9	skin damage	-	X	basal cells of epidermis[f]
10	cataracts	-	X	lens of the eye
11	sterility	-	X	ovaries/testes
12	microcephaly	-	X	fetus[c]
13	mental retardation	-	X	fetus[c]
	Late Somatic Effects			
14	leukemia	X	-	red bone marrow
15	bone cancer	X	-	bone
16	breast cancer	X	X	breast
17	lung cancer	X	X	lung
18	gastrointestinal cancer	X	X	lower large intestine
19	thyroid cancer	X	X	thyroid
20	skin cancer	-	X	face
21	other cancers	X	X	
22	leukemia -in utero	X	-	fetus[c]
23	other cancers -in utero	X	-	fetus[c]
24	benign thyroid nodules	-	X	thyroid
	Genetic Effects			
25	single gene - dominant	-	X[g]	ovaries/testes
26	single gene - X-linked	-	X[g]	ovaries/testes
27	chromosome - numerical aberration (aneuploidy)	-	X[g]	ovaries/testes
28	chromosome - structural aberration (unbalanced translocations)	-	X[g]	ovaries/testes
29	multifactorial diseases	-	X[g]	ovaries/testes

[a] There is no clear differentiation between the hematopoietic and prodromal syndromes. Lushbaugh (1982) defines all symptoms between anorexia and death as "acute hematologic syndrome". The symptoms considered by Lushbaugh include anorexia, nausea, vomiting, fatigue, and diarrhea. Our models permit prediction of each of these symptoms. However, in our taxonomy, they are identified as prodromal symptoms.

[b] Dose to small intestine is important for brief exposure. Dose to lower large intestine is important for protracted exposure.

[c] Technically, it is the dose to the embryo or fetus depending upon the stage of development. For the first 7 weeks, or 50 days, the term "embryo" is appropriate.

[d] Midline, midplane upper abdominal dose.

[e] Although not originally identified as a separate health effect of interest, a model was developed for thyroid ablation. See footnote "e" of Table 2.3.

[f] For a depth of 0.1 mm and an area of 35 to 100 cm^2.

[g] Incidence of each type of genetic effect is modelled. Fractions of each class of defect that is fatal are also given.

dose is received will exhibit the stated effect. By accounting for the birth rate (probability per unit time) and integrating over all future generations, genetic risks may also be expressed as probabilities.

For many radiation-induced health effects, sensitivities are quite variable among the population and may depend upon age, gender, or race, as well as other factors. Where these factors are understood, they are discussed, and to the extent possible, quantified. However, all final numerical models predict the fraction of a cohort with the age, gender, and race structure of the 1980 U.S. population that would be expected to experience the effect. For example, if the two genders have different sensitivities:

$$R\,(d) = w_m\, r_m\,(d) + w_f\, r_f\,(d) \qquad (1.1)$$

where $R(d)$, the final dose-response model is a weighted average of the dose-response models for males, $r_m\,(d)$, and for females, $r_f\,(d)$. The weights, w_m and w_f are taken from the 1980 Census of the United States (Bureau of Census, 1983) and are summarized in Appendix A.

The models for early and continuing effects, late somatic effects, and genetic effects are presented in Volume II of this report. In that volume, the scientific basis for each model is described and the rationale for various model assumptions is explained. In Chapter 2 of this volume the models are described (*without justification*) in adequate detail to support development of computer codes for accident consequence analysis.

1.4 Scientific Basis for Risk Estimates

Where available, results of epidemiological analysis of human data have been used. The models for cancers, thyroid effects, and most early effects are based on human data. In some cases adequate human data were not available. In these cases, we have relied on toxicologic data from animal experiments. The models for genetic effects, and certain aspects of the models for early effects, are based on animal data.

To understand the dilemmas faced in any attempt to develop radiological health consequence models, one must appreciate the limitations of each source of data. The three main sources of human data used in this report are the bombing of Hiroshima and Nagasaki, medical diagnostic and therapeutic uses of radiation, and radiation accidents.[1]

Most of our models for cancer have been based largely upon analysis of cancer incidence and mortality in the survivors of the bombings at Hiroshima and Nagasaki. This data base is preferred because it involves a very large population that has been carefully followed for almost forty years. There are, however, several issues that complicate the interpretation of these data. First, the population that *survived* the bombings may not be representative of the general population. Second, the dose was received at a high dose rate. Third, the dose estimates are at this time somewhat tenuous and are undergoing revision. Fourth, the spontaneous rates of some cancers in the Japanese population are quite different from those in the U.S. population.

Where available, data from human diagnostic and therapeutic exposures have been used in conjunction with or instead of Japanese data. For example, data from a New York study

[1] A fourth potential source of human data is information on the risks observed in populations, such as uranium miners, occupationally exposed to radiation. Due to the controversy over the relative biological effectiveness (RBE) of alpha particles compared to gamma rays, these data were not relied upon in developing our models.

of women treated with x-rays for postpartum mastitis and from a Massachusetts study of women given fluoroscopic chest examinations were the basis for our model for breast cancer. Data from the ankylosing spondylitis patients were considered in conjunction with the Japanese data in the development of models for both lung and gastrointestinal cancer. The models for thyroid cancer are based primarily on analysis of data obtained by follow-up of people treated with external x-irradiation in childhood for benign thyroid disease. There are certain advantages of data from therapeutic and diagnostic exposures. Often relatively large populations are involved and the doses involved tend to be relatively well known. However, therapeutic and diagnostic doses are often administered according to schedules that generate patterns of dose and dose rate quite different from those expected to follow a nuclear power plant accident. Interpretation of data from therapeutic exposures is further complicated by the fact that the individuals irradiated are under the care of a physician, are not in normal health, and may have received treatments other than irradiation.

Estimates of the median lethal (or effective) doses for some early effects have been based largely upon analysis of data involving therapeutic exposures of terminally ill cancer patients. These data have been supplemented by data from the population of Rongelap atoll — exposed during the detonation of a nuclear device at Bikini — and by data on the approximately thirty individuals who have received significant whole-body exposure in various radiation accidents. Accidental exposures commonly involve small numbers of otherwise healthy middle-aged males. Because of the small numbers of individuals involved, these accident data are relatively uninformative. In particular, they cannot be expected to provide precise information about the extremes of the distribution of risk. Interpretation of data from accidental overexposure is often further complicated by limited knowledge of the doses and dose rates involved, and by the fact that most accident victims receive extensive individual medical care.

The models for genetic effects and some aspects of the models for early effects have been based upon data from experiments involving animals. The estimates of the gametic induction rates for dominant and x-linked genetic effects have been based upon observation of skeletal defects in the offspring of irradiated mice. The estimate of the gametic induction rate for translocations involved analysis of translocations observed in primary spermatocytes of humans and marmosets. The slope of the dose-response curve for death from hematopoietic syndrome and the parameters of the dose-response models for death due to pulmonary syndrome following protracted exposure have been based upon effects observed in beagle dogs. In these experimental settings, relatively large populations may be involved and doses are well known. As a result, it is frequently possible to determine accurately the dose-response curves appropriate for the animal species involved in the experiment. However, there is a certain inevitable uncertainty in any extrapolation from one species to another. A further complication is introduced by the common use of inbred colonies of laboratory animals. Inbreeding reduces heterogeneity and is likely to result in steeper dose-response functions than those appropriate for heterogeneous human populations.

In summary, although every attempt has been made to use the best possible data, the available data do not permit precise prediction of the health consequences of exposure to radiation. Because much of the data concerns exposure at high doses and dose rates, it is particularly difficult to estimate the risks expected at much lower doses and dose rates since

this involves the use of models that cannot be validated. Even at high dose and dose rate there may be uncertainties because of the need to extrapolate from one population (or species) to another.

1.5 Uncertainties: Estimation and Expression

The health effects caused by radiation cannot be predicted precisely. The statement of work reflected an awareness of this (Sandia, 1983). The improved health effects models were to provide:

> . . . a realistic (i.e., "best estimate") assessment of the health effects and risks due to the radiation dose levels and types expected from nuclear reactor accidents. The uncertainties associated with each health effect relationship shall be described and, to the extent possible, quantified. For those cases where the uncertainty can't be fully quantified, upper and lower bounds should be estimated.

Perhaps the most important component of this charge is the request for *realistic* estimates. The central estimates given in this report are intended to represent the most likely values, i.e., they are not thought to be either over- or under-estimates. However this claim should not be overinterpreted. The central estimates are between the upper and lower estimates and they are thought to be realistic by our Working Groups and Advisory Group, but there is no objective basis for demonstrating that they are "most likely".

In certain areas there are large uncertainties. In these areas central estimates are of little value unless accompanied by estimates of the magnitude of uncertainties.

In the presence of uncertainty it would be most useful to specify the conditional probability density function for risk as a function of dose and any modifying factors, e.g., dose rate. Figure 1.1 depicts this ideal. With such complete information, one could readily determine any of several parameters (median, mode, mean, [1-α]% confidence limits) of the distribution of risk for any dose. And if an appropriate utility function were available, one could use techniques from statistical decision analysis to establish a "certainty equivalent risk", i.e., the risk that, if known perfectly, would be viewed as equivalent in severity to the specified probability density function for risk, for any level of dose. Lacking this complete specification of uncertainty, one would want several parameters of the estimated distribution of risk, for example, the median and the upper and lower limits of a specified (e.g., 95%) confidence interval.

The uncertainties in modelling health risks are of two types. The first are uncertainties in parameter estimation. These arise due to the random nature of the processes in question and are amenable to statistical analysis. If this were the only source of uncertainty, complete objective descriptions of uncertainty might be possible. However, there are many other sources of uncertainty, such as extrapolation of risks from one species (or population) to another, the choice of models for interpolation of risks from those observed at high doses and dose rates to those anticipated at low doses and dose rates, and estimation of the contribution of sensitive subgroups to the expected risk for the population of interest. The confidence intervals given by standard statistical algorithms reflect only the random errors. Thus, the overall uncertainty in prediction is almost always larger than indicated by the ordinary statistical confidence intervals.

Estimation of the magnitude of this second type of uncertainty is not simple. It involves unavoidably subjective elements. For example, a complete analysis of uncertainty for the

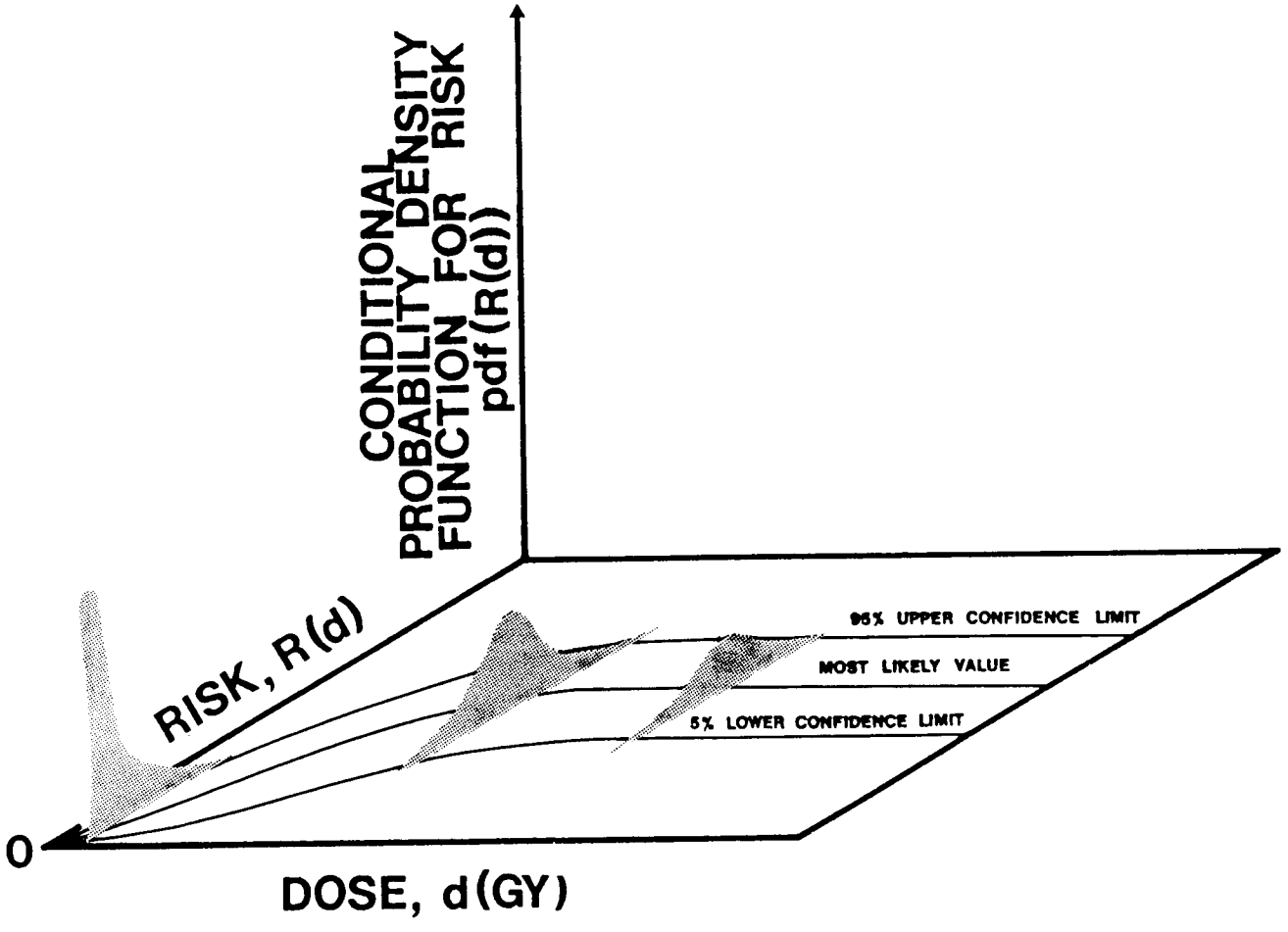

Figure 1.1 Ideal model output under uncertainty: probability density function for risk conditional on dose.

low-dose extrapolation problem would involve enumeration of all candidate models and estimation of the probability that each of the models was the "true" model. The required probabilities would have to be subjectively estimated. It is to be expected that the subjective probability estimates would vary considerably from expert to expert and therefore would be of little use without a mechanism for combining the estimates. To achieve such a combination of estimates a method would be required for assigning weights to the individual estimates.[2] This would be controversial, outside the scope of work of this project and beyond the areas of expertise of the group assembled.

We have attempted to sidestep this issue by giving, in addition to the central estimate, an upper estimate and a lower estimate. These upper (and lower) estimates should not be considered as resulting from the set of assumptions that would lead to the highest (or lowest) possible estimates. They also should not be regarded as confidence limits, since it is not feasible to associate with them a probability. Rather, they are intended to reflect alternative assumptions that are reasonably consistent with available evidence, and that may be preferred by some scientists.

We are aware that this is not a wholly satisfactory approach from the point of view of a policy analyst or decision maker. The uncertainty estimates given here should be regarded as a first approximation to the truth. We recommend that the treatment of uncertainty be refined in a subsequent effort that utilizes the expertise of professionals trained in the areas of quantitative decision analysis and subjective probability assessment.

1.6 Aggregate Measures of Health Effects

A wide variety of radiation-induced health effects may occur in a population exposed to radiation and radionuclides accidentally released from a nuclear power plant. The effects vary substantially in severity and in timing. The models presented in this report permit a rather detailed examination of the health effects projected to result from an accident.

The computer codes now used to predict the health consequences of nuclear power plant accidents provide, as summary measures of health risks, the numbers of early and late deaths, early and continuing illnesses, thyroid effects, and genetic effects.

For some purposes it may be necessary to summarize the health impact using only one or two measures. One possible approach would be simply to add all effects. Such a simple-minded approach is unlikely to achieve widespread acceptance because it ignores differences in both the severity and timing of effects.

An alternative approach, which reflects timing as well as severity, involves:

$$I = \sum_i \sum_j \omega_i \, \omega_j \, n_{ij} \tag{1.2}$$

where I is an aggregate index of health impact, ω_i is a severity weight applicable to the ith type of effect, ω_j is a time-dependent weight applicable to effects that occur in the jth time period, and n_{ij} is the number of effects of type i expected to occur in time period j.

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[2] There has been some recent work in this area that appears promising. For example, Hofer (1985) has derived weights by analysis of the self- and peer-ratings of experts.

To calculate this index one must first assign the severity and timing weights, ω_i and ω_j, to all projected effects. One measure of the relative severity of various causes of death is their impact on life expectancy.[3] This simple measure of severity is attractive because it is easy to calculate and is objective. However, it does not reflect variations in the duration or severity of periods of illness or disability.

Typically, life expectancy is calculated as:

$$e_x = p_x + p_x p_{x+1} + \cdots + p_x p_{x+1} \cdots p_{x+k} \qquad k \to \infty \tag{1.3}$$

where p_x is the probability that a person of age x will survive to his or her $x+1$st birthday, and e_x is his or her remaining life expectancy. In this formula each year of life is given *equal* weight. By introducing a set of quality-of-life factors, ω_x, the quality-adjusted life expectancy can be calculated:

$$e_x^Q = \omega_x p_x + \omega_{x+1} p_x p_{x+1} + \cdots + \omega_{x+k} p_x p_{x+1} \cdots p_{x+k} \qquad k \to \infty \tag{1.4}$$

Here the factors, ω_x, are numbers between zero and one reflecting the severity of symptoms and disabilities, one corresponding to perfect health and zero corresponding to death. Changes in quality-adjusted life expectancy calculated in this way reflect both reductions in length of life and quality of life, and are expressed in quality-adjusted-life-years (QALYs).[4]

An approximate estimate of the reduction of quality-adjusted life expectancy, Δe_i^Q (QALY/case), may be made using:

$$\Delta e_i^Q = f_i \Delta e_i + (1-\omega_i)\, y_i \tag{1.5}$$

where f_i is the fraction of cases which are fatal, Δe_i is the reduction in life expectancy (yr/death), ω_i is the typical quality-of-life factor (QALY/yr), and y_i is the typical duration of symptoms or disability (yr/case) for effect i. Table 1.2 summarizes the information available for making these estimates. Deaths due to early effects typically occur within a month or so of exposure and their impact on effective life expectancy is essentially equal to the reduction in life expectancy that they cause. Late somatic effects are likely to be diagnosed several years before the deaths occur. Thus the impact of cancers is somewhat greater when measured in terms of their effect on quality-adjusted life expectancy. Although there is a rapidly developing literature on health status indicators, quality-of-life factors for cancers have not been reported in the open literature.[5] Therefore we have simply given a range of reductions in effective life expectancy, corresponding to assigning severity factors from zero to one to the years between diagnosis and death. The apparent impact of genetic disease increases substantially when quality-adjusted life expectancy is used as a measure of impact.

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[3] Examples of the use of life table methods in the evaluation of radiation risks are found in Bunger *et al.* (1981) and Davis (1977).

[4] For a discussion of the basic issues involved in deriving summary measures of health effects the reader is referred to Raiffa (1977).

[5] For further discussion of this topic, the reader is referred to McNeil (1981), Kaplan (1982), Sackett (1978), and Pochin (1977). It is our understanding that Sir Edward Pochin is revising the ICRP report on developing an "index of harm". Any major revisions should be reflected in the revised accident consequence codes.

Table 1.2 Average Reduction in Quality-Adjusted Life Expectancy for Each Cause of Death

Index (i)	Effect	Reduction in Life Expectancy[a] (yr/case) $f_i \Delta e_i$	Duration of Symptoms/Disability (yr/case) y_i	Severity Weight (QALY/yr) $(1-\omega_i)$	Reduction in Effective Life Expectanc (QALY/case) Δe_i^Q
	Early and Continuing Effects				
1	Hematopoietic Syndrome	43.8	0	n/a	43.8
2	Pulmonary Syndrome	43.8	0	n/a	43.8
3	Gastrointestinal Syndrome	43.8	0	n/a	43.8
4	Pre- and Neo-Natal Deaths	73.3	0	n/a	73.3
	Late Somatic Effects				
14	Leukemia	34.9	0[b]	n/a	34.9
22	-in utero	67.3	0[b]	n/a	67.3
15	Bone Cancer	34.9	0[b]	n/a	34.9
16	Breast Cancer	3.8	12.0[c,d]	?	3.8-15.8
17	Lung Cancer	13.0	1.7[c,d]	?	13.0-14.7
18	Gastrointestinal Cancer	6.9	5.3[c,d]	?	6.9-12.2
19	Thyroid Cancer	2.6	23.6[c]	?	2.6-26.2
21	Other Cancer	6.7	8.2[c,d]	?	6.7-14.9
23	-in utero	68.3	0[b]	n/a	68.3
	Genetic Effects				
	Single Gene Dominant				
25	-non X-linked	13	25	0.33	21
26	-X-linked	28	40	0.40	44
	Chromosome Defects				
27	-numerical (aneuploidy)	24	44	0.50	46
28	-structural (unbalanced translocations)	50	20	0.95	69
29	Multifactorial	30	20	0.25	35

[a] Approximated as the product of fraction of cases that are fatal and the loss of life expectancy per fatal case (yr/death). The fractions of cancer cases assumed to be fatal are: leukemia (100%), leukemia in utero (100%), bone cancer (100%), breast cancer (24%), lung cancer (91%), gastrointestinal cancer (59%), thyroid cancer (10%), other cancer (51%), other cancer in utero (100%). The basis for the assumptions leading to these values is found in Chapter 2, Volume II.

[b] Actually, there is some time between incidence and death; however, our models for these diseases assume all cases are immediately fatal. This may result in a slight overestimation of mortality and underestimation of morbidity, but should not substantially influence the total reduction in effective life expectancy.

[c] These numbers are simply the expected time between incidence and death. For some diseases, such as thyroid cancer, surgical removal of the tumor may effectively mitigate any symptoms of disease.

[d] Although these estimates have not been derived by explicit analysis of the survivorship functions for various cancers, they are qualitatively consistent with results recently reported by NCI (1983). For example, the NCI gives the following 5-year survival rates: breast (73%), lung (12%), colon (50%), rectum (50%), stomach (15%), thyroid (92%), and cancer of all types (48%).

To account for differences in the timing of effects, some analysts may wish to assign different weights to effects according to the time of their occurrence. The most commonly used time-dependent weights are from the geometric series:

$$\omega_j = \frac{1}{(1+\rho)^{t_j}} \tag{1.6}$$

where ω_j is the weight applicable to the jth time interval, ρ is typically--but not necessarily--a positive number, and t_j is the number of time units (yr) to the midpoint of the j^{th} time interval. In economic analysis, ρ would be called the real discount rate, and the value of a series of cash flows, weighted by the ω_js, would be called its present value. Typical values of ρ are between 0 and 0.1.[6]

Although summarization of the health effects of an accident using aggregate indices may be desirable, use of these measures would be controversial. Although there is a growing literature on health status indices, these indices are not widely used at this time. The assignment of severity weights introduces subjectivity into the analysis. The application of discounting methods to evaluation of health effects raises ethical issues. On the other hand, common summary measures such as the number of genetic or somatic effects implicitly treat all effects within a class (cancers) equally. This choice of $\omega_i = 1$ and $\omega_j = 1$ is no less arbitrary or subjective than those involved in the evaluation of I.

Due to these and other considerations, we recommend that the computer codes developed for implementation of our models be designed to incorporate arbitrary severity and time-dependent weights, ω_i and ω_j. However, any summary indices should be provided as complements to (rather than substitutes for) detailed disease and time-specific consequence model output.

1.7 Summary

Improved health effects models have been developed that address most of the concerns expressed in the critical review.

The new models for early effects account for the influence of dose rate and accommodate the limited knowledge of variations in the sensitivities of adults and children. They include estimates of risks of mental retardation, skin burns, and sterility — effects that were not included in previous computer codes.

The new models for late somatic effects reflect information from the BEIR III report (1980) and the ongoing follow-up of the survivors of the bombings of Hiroshima and Nagasaki. Linear or linear-quadratic models replace the piecewise-linear models used in the Reactor Safety Study. Where appropriate, absolute risk models have been replaced by relative risk models and 30-year plateaus have been replaced by lifetime plateaus. The models include estimates of morbidity as well as mortality. Because the cancer models are based largely upon data from Hiroshima and Nagasaki, they will have to be re-evaluated as soon as the revised dosimetry becomes available.[7]

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[6] Discounting radiation-induced health effects is discussed in Clark (1981).

[7] Preliminary reanalyses of these data indicate that the cancer risk estimates may increase by a factor of approximately 1.5 to 2 when the revisions in dosimetry are accounted for (Jablon, 1984).

The new models for genetic effects are consistent with the most recently reported findings from studies of the descendants of the survivors at Hiroshima and Nagasaki. Linear-quadratic models have been used. The parameter estimates are based on the assumption that gametic induction rates in male and female germ cells are equal. More recent demographic data and more sophisticated methods of demographic analysis have been used to develop the new models.

The models for both somatic and genetic risks have been developed in such a way that the dynamics of population risks may be analyzed. Estimates of life-years lost and duration of illness have been generated and framework has been recommended for summarizing health impacts. Uncertainty has been addressed by providing models for upper, central, and lower estimates of most effects.

Although there are certain limitations of the new models — they only apply to low-LET radiation; the uncertainty estimates are only approximate; they do not provide estimates of genetically-induced spontaneous abortions;[8] the influence of area irradiated is not explicitly accounted for in the models for skin burns — they represent a significant improvement over the Reactor Safety Study models and can easily be modified to reflect any advances in our understanding of the health effects of radiation.

[8] The decision not to model genetically-induced spontaneous abortions was based largely upon the recommendation of our Advisory Group. After further consideration of the issue, we believe our original decision was incorrect and have recommended that the NRC develop models that would address this issue.

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Chapter 2

MODEL DESCRIPTION

2.1 Introduction

A primary goal of our effort was to produce health effects models that would enable one to predict the number of health effects expected as a function of time following an accident at a nuclear power plant. In this chapter we summarize the models developed by the Working Groups and illustrate how they are intended to be applied to estimate the numbers of early and continuing effects, late somatic effects, and genetic effects that would be expected to occur following an accident. The discussion begins with a description of the models for central estimates of effects and then considers the modifications of these models that are required to derive upper and lower estimates.

2.2 Models for Central Estimates

The models for central estimates include those for early and continuing effects, somatic effects, and genetic effects.

2.2.1 Early and Continuing Effects

Early and continuing effects have been modeled using hazard functions. Mathematically a hazard function has the form:

$$r = 1 - e^{-H} \tag{2.1}$$

where r is the probability that a person will exhibit the effect of interest, and H is a function of the dose received by the person.[1, 2] Figure 2.1 illustrates the relationship between H and r for a hazard function. The relationship between dose and risk is implicit in the relationship between dose and hazard. The cumulative hazard functions used to predict early effects have the form:

$$H = 0.693 \left\{ \frac{d}{\alpha} \right\}^{\beta} \tag{2.2}$$

where H is the cumulative hazard, d is the (mean absorbed) dose to the organ of interest, and α and β are model parameters.[3]

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[1] To distinguish between the risk to an individual of a specific age, gender, and/or race and the population risk (i.e., the fraction of a cohort with the age, gender, and racial structure of the 1980 U.S. population expected to experience the effect), lower case r has been used for individual risk and upper case R for population risk.

[2] The symbol H is used in this report to represent cumulative hazard. This is consistent with the literature on statistics of failure time data. However, in radiation protection the symbol H is normally used to represent the dose equivalent.

[3] Mathematically, the risk predicted by a hazard function is positive for any non-zero level of dose. Biologically there are reasons to believe that non-stochastic radiation effects are threshold effects, i.e., there is some dose below which there is no risk. For values of β above 2, hazard functions exhibit virtual thresholds (i.e., they rapidly approach zero for doses below α). Nonetheless, because of the threshold nature of nonstochastic effects, it is recommended that risks calculated to be below 0.005 be treated as zero. This choice, while somewhat arbitrary, is intended to prevent nonsensical estimates of early deaths and disease in large populations exposed to doses well below the LD_{50} or ED_{50}.

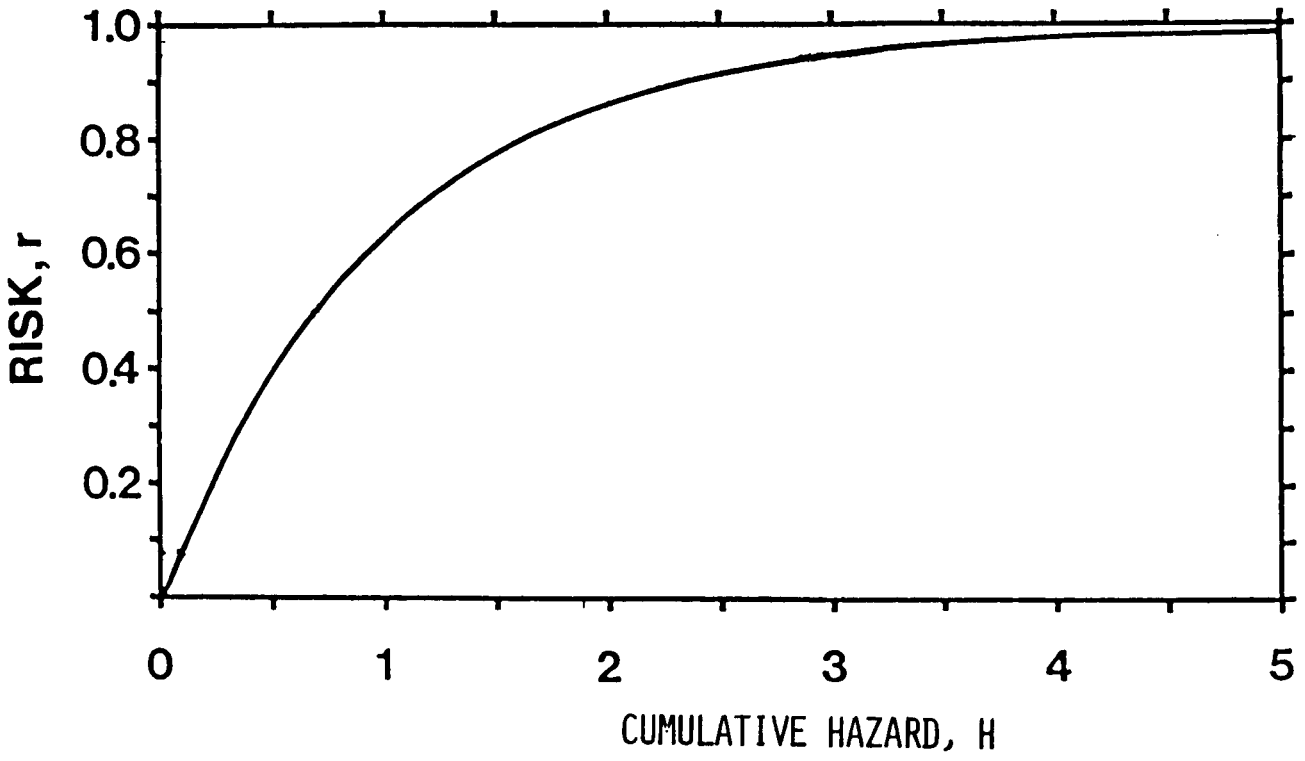

Figure 2.1 Relationship Between Cumulative Hazard, H, and Risk, r.

The four early causes of death for which hazard functions have been developed are the hematopoietic syndrome, pulmonary syndrome, gastrointestinal syndrome, and pre- and neonatal exposure. The values of α and β to be used in models for central estimates of these effects are given in Table 2.1.[4]

Because adults and children are thought to have different sensitivities to the early effects of radiation, two sets of values of the model parameters are required: one for adults and one for children. According to the 1980 Census of the United States, children (persons 18 years old or younger) comprise approximately 30% of the population. Therefore, to estimate the fraction of a cohort with the age structure of the 1980 U.S. population that will experience an early effect, it is necessary to construct a weighted average of the appropriate risks:

$$R \approx 0.30\,(1-e^{-H_c}) + 0.70\,(1-e^{-H_a}) \tag{2.3}$$

where R is the population risk, and H_c and H_a are the cumulative hazard functions for children and adults, respectively. The working group on early effects concluded that, with the exception of the pulmonary syndrome, available data do not permit reliable estimation of separate parameters for adults and children. For pulmonary syndrome children are thought to be twice as sensitive as adults, i.e., $\alpha_{child} \approx \alpha_{adult}/2$. The parameter estimates shown in Table 2.1 for pulmonary syndrome have been adjusted to predict the risk in a mixed population of adults and children. Although the parameter estimates developed for the hematopoietic and gastrointestinal syndrome are believed to be appropriate for adults, they may underestimate (to an unknown degree) the risks in a cohort of mixed ages.

Similarly, the effect of radiation upon the probability of pre- and neonatal death depends upon the exact stage of development of the fetus/embryo. This leads to an equation of the form:

$$r \approx f_0(1-e^{-H_{40}}) + f_1(1-e^{-H_{41}}) + \ldots + f_k(1-e^{-H_{4k}}) \tag{2.4}$$

where r is the risk to a "typical" fetus, and f_0, f_1 . . . f_k are the fractions of pre- and neonates in each of the k stages of development for which hazard functions have been generated. The parameter estimates given in Table 2.1 for pre- and neonatal death are appropriately weighted to reflect the average risk to a pre- or neonate. To determine the number of pre- and neonatal deaths, it is necessary to multiply the resulting risk, r, by the number of pre- and neonates within the population. Very approximately, the number of pre- and neonates may be estimated as 1% of the exposed population.

Because the effectiveness of a specified dose for induction of early effects depends upon dose rate, the hazard functions for early effects involve weighted sums of the doses received within various time intervals following an accident. For example, the hazard function for the pulmonary syndrome is:

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[4] In Table 2.1, and throughout the chapter, the index i is used to identify unambiguously the effect being considered.

Table 2.1 Model Parameters for Central Estimates of Early Mortality

Index, i	Effect	Shape Parameter, β_i (dimensionless)	Location Parameter,[e] α_{ij} (Gy) For Various Time Intervals, t_j (day) After an Accident					
			0-1	1-7	7-14	14-21	21-30	30-200	200-365
1	hematopoietic syndrome								
	minimal treatment	10	3.4	←7→		←14→		-	-
	supportive treatment	6.6	4.5	←[9]→		←[18]→		-	-
	intensive treatment[a]	6.6	11	-	-	-	-	-	-
2	pulmonary syndrome[b]								
	minimal treatment	3.0	8.0	←80→		←185→			450
	intensive treatment[c]	3.0	16.0	←160→		←370→			900
3	gastrointestinal syndrome								
	minimal treatment	10	15	35	-	-	-	-	-
	supportive treatment[c]	10	45	105	-	-	-	-	-
4	prenatal/neonatal deaths[d]	3	1.0	-	-	-	-	-	-

[a] In the Reactor Safety Study, intensive treatment was referred to as "heroic treatment".

[b] The parameters shown are for a mixed population of adults and children.

[c] Intensive treatment for pulmonary syndrome (lung lavage) and supportive treatment for gastrointestinal syndrome (laxative) actually reduce the doses received, but for modelling purposes an equivalent result is obtained by using modified model parameters, i.e., α_{ij}.

[d] The parameters given here were obtained by applying equation (2.4) to data given in Chapter 1, Volume II. As such, they represent a weighted average of the response of pre- and neonates in various stages of development. The risks predicted using this equation would have to be multiplied by 0.01 to be applicable to the general population because the number of pre- and neonates is approximately 1% of the general population.

[e] Dashes in the body of this table indicate that the Early Effects Working Group provided no estimate of α applicable for this time interval. If appreciable dose occurs in these intervals, as a first approximation the highest α value in the row could be used to estimate risks.

$$H_{2a} = 0.693 \left[\frac{d_{21}}{8} + \frac{d_{22}}{80} + \frac{d_{23}}{185} + \frac{d_{24}}{450} \right]^{2.5} \tag{2.5}$$

where d_{21} is the dose received within the first day; d_{22} is the dose received between the 1st and 14th day; d_{23} is the dose received between the 14th and 200th day; and d_{24} is the dose received between the 200th and 365th day.[5]

The probability of death due to the hematopoietic syndrome is thought to depend upon the nature of the medical treatment that is obtained. Therefore, three hazard functions have been developed for the hematopoietic syndrome: one appropriate for minimal medical treatment, one for supportive treatment, and one for intensive treatment.[6] If the fractions of the exposed adult population receiving these various treatments are f_m, f_s, and f_i, then the risk in the cohort would be:

$$R = f_m(1-e^{-H_{1m}}) + f_s(1-e^{-H_{1s}}) + f_i(1-e^{-H_{1i}}) \tag{2.6}$$

It is anticipated that virtually all persons with high acute exposures would receive, at least, minimal medical treatment, and that very few would receive intensive treatment. However, there is considerable uncertainty about the number who could receive supportive treatment.[7]

The dose to lung from inhaled radionuclides, and therefore the risk of death from the pulmonary syndrome, may also be influenced by medical treatment. Therefore two hazard functions have been developed for pulmonary syndrome: one for minimal treatment and one for intensive treatment.

To determine the overall mortality risk from the exposure of several organs, one simply sums the cumulative hazard functions:

$$r = 1-e^{-(H_1 + H_2 + H_3)} \tag{2.7}$$

where r is the individual mortality risk, H_1 is the cumulative hematopoietic hazard, H_2 is the cumulative pulmonary hazard, and H_3 is the cumulative gastrointestinal hazard. In principle there might be synergisms due to the effects of damage to one organ on the ability of another organ to respond to radiation-induced injury. Although these interorgan hazard functions

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[5] It should be noted that although this approach for adding brief and protracted dose appears to be reasonable, it has not been verified with human data. As shown in Scott (1984), it leads to higher risk estimates than alternative approaches that assume the effects of brief and protracted dose are independent.

[6] Intensive treatment was referred to as heroic treatment in the Reactor Safety Study.

[7] Where possible, site-specific data on the availability of supportive medical treatment should be used to determine f_s. However, such data are often not readily available. See, for example, Anderson (1982). Lacking such data, as a generic approach, it would seem reasonable to use a single dose-response function midway between that for minimal and supportive treatment. The parameter values appropriate for such a curve would be: $\alpha = 4$, $\beta = 6$ for dose received within 1 day of an accident; $\alpha = 7.5$, $\beta = 6$ for dose received between 1 and 14 days after an accident; and $\alpha = 15$, $\beta = 6$ for dose received between 14 and 30 days after an accident.

cannot be mathematically estimated, it is believed that the hematopoietic hazard function parameters reflect some of the interorgan effects.

The effects of acute exposures to high doses of radiation are not limited to mortality. Several forms of morbidity may also occur. To account for these, hazard functions have been developed for prodromal symptoms (anorexia, nausea, fatigue, vomiting, and diarrhea), radiation pneumonitis, hypothyroidism, acute radiation thyroiditis, temporary sterility in males, permanent sterility in females, erythema, transepidermal injury, microcephaly, and mental retardation.[8] The parameters of these functions are summarized in Table 2.2.

2.2.2 Late Somatic Effects

The late somatic effects have been modeled using either linear or linear-quadratic dose-response functions. Mathematically these have the form:

$$r(\tau,d) = \alpha_\tau d \tag{2.8}$$

$$r(\tau,d) = \alpha_\tau d + \beta_\tau d^2 \tag{2.9}$$

where $r(\tau,d)$ is the risk of cancer incidence or mortality per unit time τ time intervals after receiving a dose, d is the (absorbed) dose to the organ of interest, and α_τ and β_τ are model parameters that are effect-specific and may be time-interval-specific. The risk given by (2.8) and (2.9) is conditional upon surviving all other causes of death for τ years. Figure 2.2 illustrates the relationship between risk and dose for a linear, and two linear-quadratic functions which predict equal risks at a dose of 1.5 Gy. Below this dose, the linear model predicts the greatest risk and the linear-quadratic models predict the least. The somatic effects Working Group recommends that above 1.5 Gy the linear model be used for all risk projections.

The eleven late somatic effects for which models have been developed are listed in Table 2.3. The table identifies the models and parameter values thought to be appropriate for predicting central estimates of these effects.

The central estimates of mortality from breast cancer, thyroid cancer, leukemia due to *in utero* exposure, "other" cancers and of morbidity from skin cancer due to *in utero* exposure, and of morbidity from benign thyroid nodules are based on linear dose-response models.

The central estimates of mortality from leukemia, bone cancer, lung cancer, gastrointestinal cancer, and "other" cancers and of morbidity from skin cancer are based on linear-quadratic dose-response models. Because it is believed that dose rate as well as dose is important in determining the likelihood of an effect, the quadratic component of these functions is to be included only when doses are received at high dose rates. Although in certain types of accidents the dose rates in some geographic areas may be high for several years after an accident, protective action guidelines will require evacuation/interdiction of these areas. The only population expected to receive doses at high dose rates is the group of people exposed to cloudshine, groundshine, and inhalation of radionuclides during passage of the radioactive plume.

[8] Although thyroid ablation was not specifically identified as a health effect of interest, a model for thyroid ablation was developed as an element of the models for predicting thyroid cancers and benign thyroid nodules. It is given in footnote "e" of Table 2.3.

Table 2.2 Model Parameters for Central Estimates of Early Morbidity

Index (i)	Effect	Shape Parameter, β_i (dimensionless)	Threshold d_{oi} (Gy)	Location Parameter,[d] α_{ij} (Gy) For Various Time Intervals, t_j (day) After an Accident							
				0-1	1-7	7-10	10-14	14-21	21-30	30-200	200-365
5	prodromal syndrome										
	anorexia	2.0	n/a	0.97	2.0	-	-	-	-	-	-
	nausea	2.0	n/a	1.4	2.6	-	-	-	-	-	-
	fatigue	2.0	n/a	1.5	-	-	-	-	-	-	-
	vomiting	3.0	n/a	1.8	4.9	-	-	-	-	-	-
	diarrhea	2.0	n/a	2.3	5.3	-	-	-	-	-	-
6	lung function impairment	3.0	n/a	4.0	←	40	→	←	90	→	225
7	hypothyroidism	1.3	2	60	n/a	n/a	n/a	n/a	n/a	n/a	n/a
			10	n/a	←	300	→		-	-	-
8	acute radiation thyroiditis	1.9	200	-	←	1200	→		-	-	-
9	effects on skin										
	erythema	5.2	n/a	6	←	10	→	-	-	-	-
	transepidermal injury	5.3	n/a	20	←	34	→	-	-	-	-
10	cataracts	7.4	n/a	3.1	←	6.2	→	←	9.3	→	
11	sterility[a,b]										
	females (permanent)	3.0	n/a	2.6	6.3	-	-	-	-	-	-
	males (transient)	10	n/a	0.7	0.4	-	-	-	-	-	-
12	microcephaly[c]	1.0	n/a	0.37	-	-	-	-	-	-	-
13	mental retardation[c]	0.8	n/a	5.6	-	-	-	-	-	-	-

[a] For permanent female sterility, the age-specific dose-response curves have been combined, weighting each by the fraction of children born to the age group. The weights were derived from 1978 U.S. Vital Statistics. Because only 1% of children are born to mothers over 40 years old, the combined function is essentially identical to the dose-response for women under 40.

[b] Risks predicted using these parameters are applicable to men or women in the age groups likely to produce children. To be applicable to the general population, the risk of permanent sterility in females would have to be multiplied by 0.35, the fraction of the U.S. population that is women between the ages of 40 and 45. Similarly, the risk of transient sterility in males would have to be multiplied by 0.40, the fraction of the U.S. population that is males over the age of 12.

[c] Risks predicted using these parameters are applicable to the in utero population and would have to be multiplied by 0.01 to be applicable to the general population.

[d] Dashes in the body of this table indicate that the Early Effects Working Group provided no estimate of α applicable for this time interval. If appreciable dose occurs in these intervals, as a first approximation the highest α value in the row could be used to estimate risks.

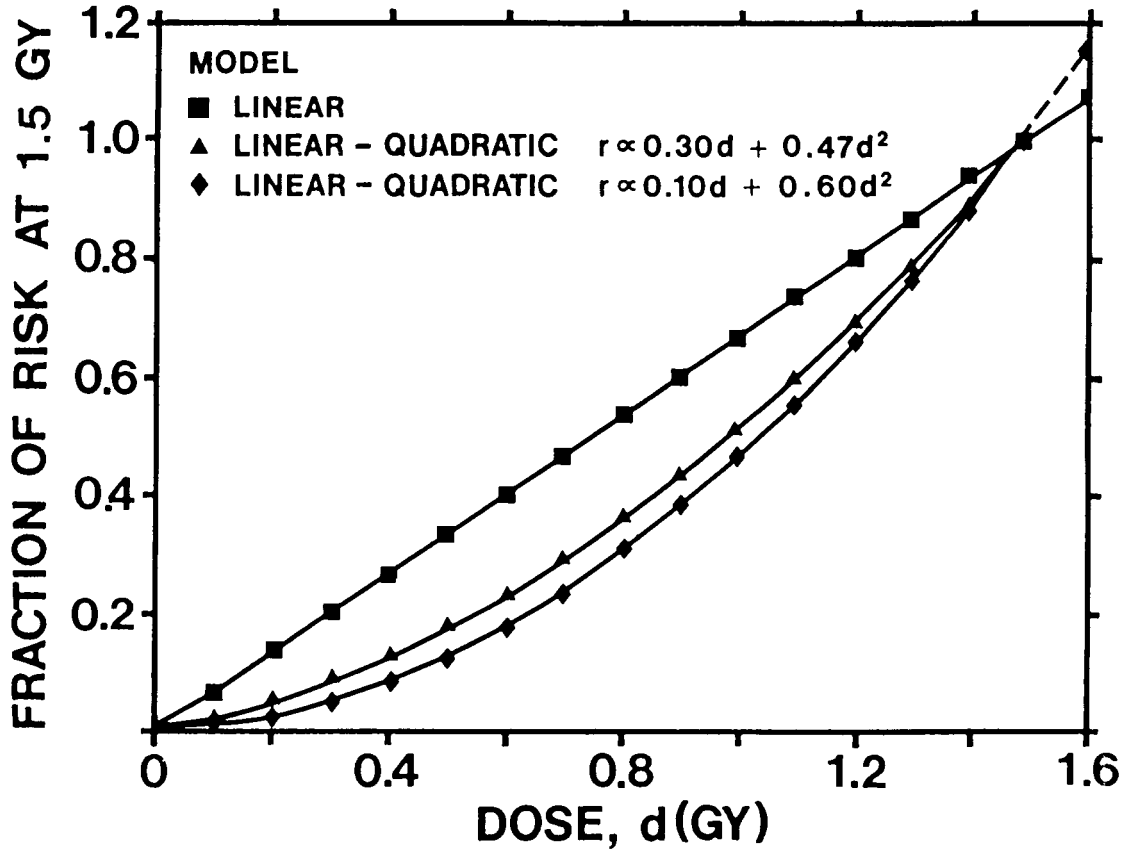

Figure 2.2 Risk as a function of dose under a linear model and two linear-quadratic models.

Table 2.3 Models and Parameter Values for Central Estimates of Somatic Risks for Individuals

Index	Effect	Type of Model	Latency	Plateau	Minimum Age	Coefficients		α	β
						Mortality	Morbidity		
14	Leukemia	Absolute, linear-quadratic	2	25	n/a	2.24×10^{-4}	n/a	0.3	0.47
15	Bone Cancer	Absolute, linear-quadratic	2	25	n/a	1.00×10^{-5}	n/a	0.3	0.47
16	Breast Cancer[a]	Relative, linear, non-age-specific	10	∞	30	45%	45%	1.0	0.0
17	Lung Cancer	Relative, linear-quadratic	10	∞	40	18%	18%	0.3	0.47
18	Gastrointestinal Cancer[b]	Relative, linear-quadratic	10	∞	n/a	39%	39%	0.3	0.47
19	Thyroid Cancer[c,d,e]	Absolute, linear age-specific gender-specific							
		$a_e \leq 18$	5	∞	n/a	2.5×10^{-5}	2.5×10^{-4}	1.0	0.0
		$a_e > 18$	5	∞	n/a	1.25×10^{-5}	1.25×10^{-4}	1.0	0.0
20	Skin Cancer	Absolute, linear-quadratic	10	∞	n/a	n/a	2.0×10^{-4}	0.3	0.47
21	Other Cancers[f]	Relative, linear-quadratic	10	∞	n/a	20%	20%	0.3	0.47
22	Leukemia - In utero[g]	Absolute, linear	0	12	n/a	2.50×10^{-3}	n/a	0.4	0
23	Other[h] - In utero[g]	Absolute, linear	0	10	n/a	2.80×10^{-3}	n/a	0.4	0
24	Benign Thyroid Nodules[c,e,i]	Absolute, linear age-gender-specific							
		$a_e \leq 18$	10	∞	n/a	n/a	9.3×10^{-4}	1.0	0
		$a_e > 18$	10	∞	n/a	n/a	4.7×10^{-4}	1.0	0

[a] These coefficients apply to the baseline breast cancer risk in women and the resultant individual risk estimates must be multiplied by 0.5 for application to the general population.

[b] Including cancers of the esophagus, stomach, colon, rectum, pancreas, and other unspecified gastrointestinal cancers.

[c] These coefficients are weighted averages of the gender-specific coefficients presented in Table A.4, Volume II.

[d] Due to the apparently lower effectiveness of internal ^{131}I dose to the thyroid, the dose recommended is: external dose + internal dose from all radionuclides except ^{131}I + 1/3 of the internal dose due to ^{131}I.

[e] To account for cell killing and eventual ablation of the thyroid, risk calculated for doses >15 Gy should be modified by the function: $e^{-0.693 \times \left(\frac{d-15}{12}\right)^2}$.

[f] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus; but excluding skin and prostate cancer and all cancers for which disease-specific risks have been modelled.

[g] These coefficients apply to the in utero population, and must be multiplied by 0.01 for application to the general population, because pre- and neonates account for about 1% of the population.

[h] Including all cancers except leukemia.

[i] Due to the apparently lower effectiveness of internal ^{131}I dose to the thyroid, the dose recommended is: external dose + internal dose from all radionuclides except ^{131}I + 1/5 of the internal dose due to ^{131}I.

Absolute risk models have been used to predict risks for seven late somatic effects. These are leukemia, bone cancer, thyroid cancer, skin cancer, leukemia (*in utero*), other cancers (*in utero*), and benign thyroid nodules. Figure 2.3 illustrates the pattern of radiation-induced mortality or morbidity as a function of time since exposure under an absolute risk model. The parameters of an absolute risk model are the latency period, l; the plateau or expression period, p; and the absolute increase in mortality or morbidity expected during the interval beginning l years after exposure and ending $l + p$ years after exposure. The plateau period may be of finite length, or the exposed individual may be assumed to be at risk for the remainder of his or her lifetime. The mortality or morbidity rate during the period of expression is assumed to be constant, but may have either a linear or linear-quadratic dependence upon dose, and may depend upon other factors such as gender, race, and/or age at exposure. Therefore, under an absolute risk model the τ subscripts for α, β, and r are unnecessary.

Relative risk models have been used to predict risks for four late somatic effects. These are gastrointestinal cancer, lung cancer, breast cancer, and other cancers. Figure 2.4 illustrates the pattern of radiation-induced mortality or morbidity as a function of time since exposure under a relative risk model. The parameters of a relative risk model are the latency period, l; the plateau or expression period, p; and the relative increase in mortality or morbidity expected during the period of expression. Although, in principle, the plateau period could be of finite length, for these four cancers it has been assumed that risks continue to be expressed for the remainder of life. The radiation-induced mortality or morbidity during the period of expression is not assumed to be constant, but instead is assumed to be a constant fraction of the baseline mortality or morbidity. The fractional increase that is expected may have either a linear or linear-quadratic dependence upon dose, and may depend upon other factors, such as age at exposure or gender. For the cancers of interest, baseline mortality or morbidity increases with age and, therefore, relative risk projections show radiation-induced risks increasing with time since exposure. Figure 2.5 shows the 1978 U.S. age-specific baseline mortality rates for breast cancer, lung cancer, gastrointestinal cancer, and other cancers. The values of α_τ and β_τ appropriate for predicting risks under a relative risk model are obtained as the product of these factors: The coefficient (% per Gy) for the effect of interest, the base-line age-specific risk for the effect of interest, and the values of α and β given in Table 2.3.

Our goal is to be able to predict the fraction of an exposed population that would be expected to develop radiation-induced cancer as a function of time since an accident. The absolute and relative risk models permit one to predict the risk, as a function of time since exposure, for an individual. Characteristics of the individual, such as gender, race, and age at exposure, influence the predicted risk. The populations likely to be exposed in the event of a nuclear power plant accident will include members of both genders, many races, and a wide distribution of ages. Therefore, to predict risks in a population, one must use demographic models in conjunction with models for prediction of individual cancer risks.[9]

The two most important demographic factors for the prediction of cancer risks are the age structure and the age-specific mortality rates in the population of interest. Figure 2.6 shows the age structure of the 1980 U.S. population, and Figure 2.7 shows the 1978 U.S. age-

[9] A standard reference on demographic modelling is Keyfitz (1971).

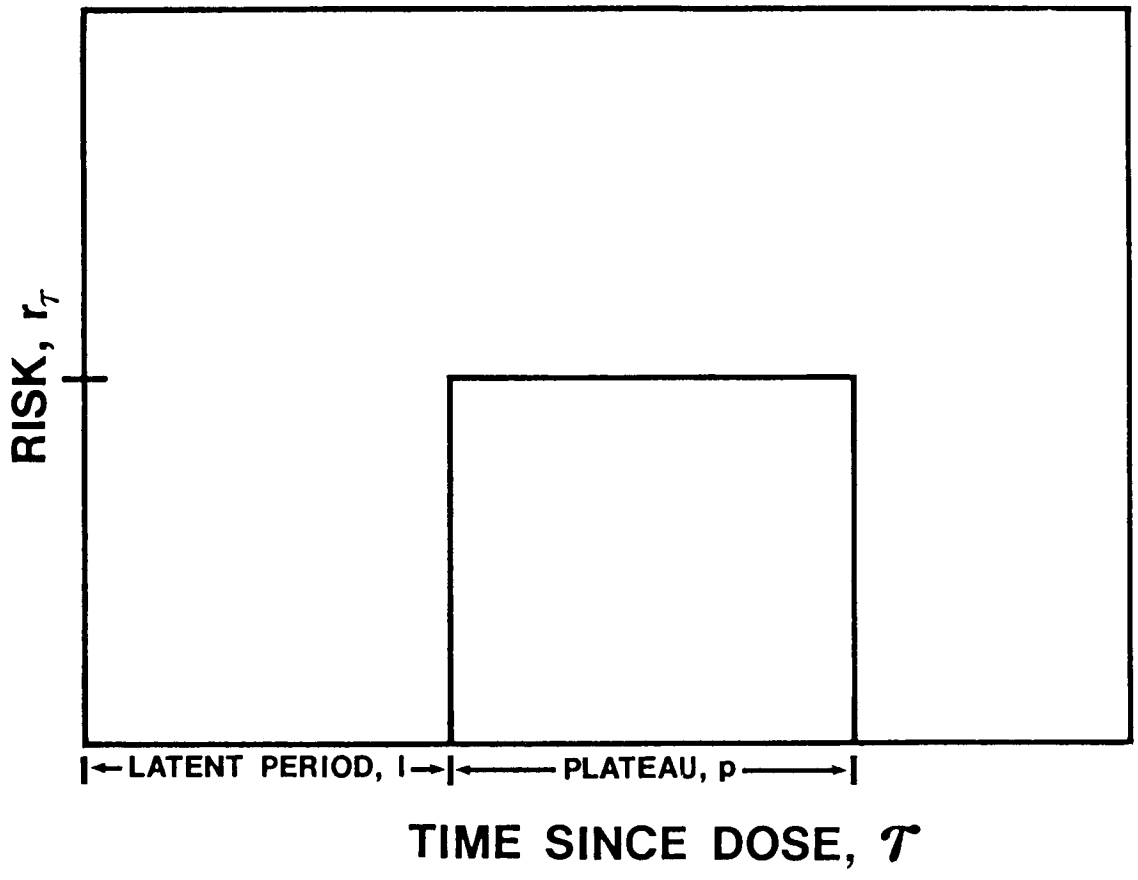

Figure 2.3 Risk as a function of time since dose under an absolute risk model.

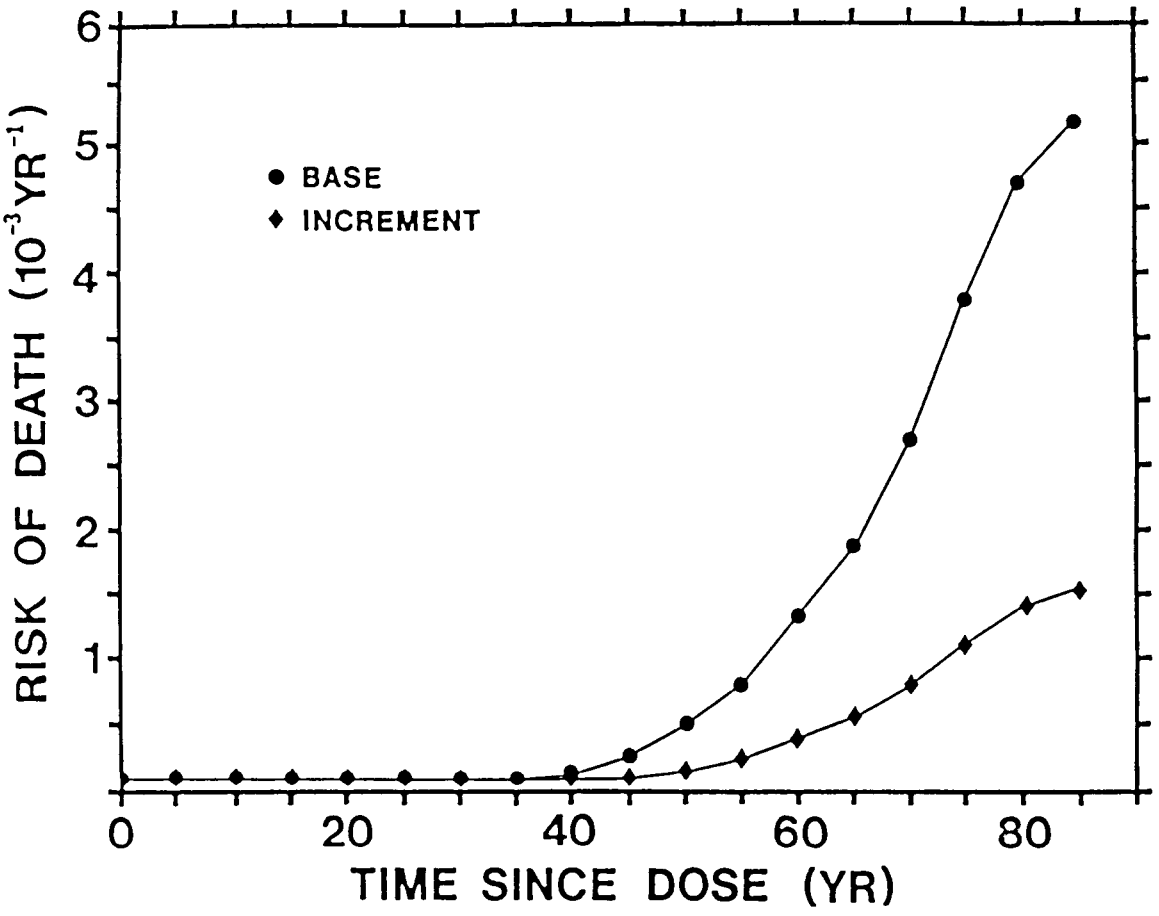

Figure 2.4 Risk as a Function of Time Under a Relative Risk Model. Data shown are for gastrointestinal cancer and for a person receiving 1 Gy to the lower large intestine at age 0-1 year. Points are plotted at the beginning of the 5-year intervals to which they apply.

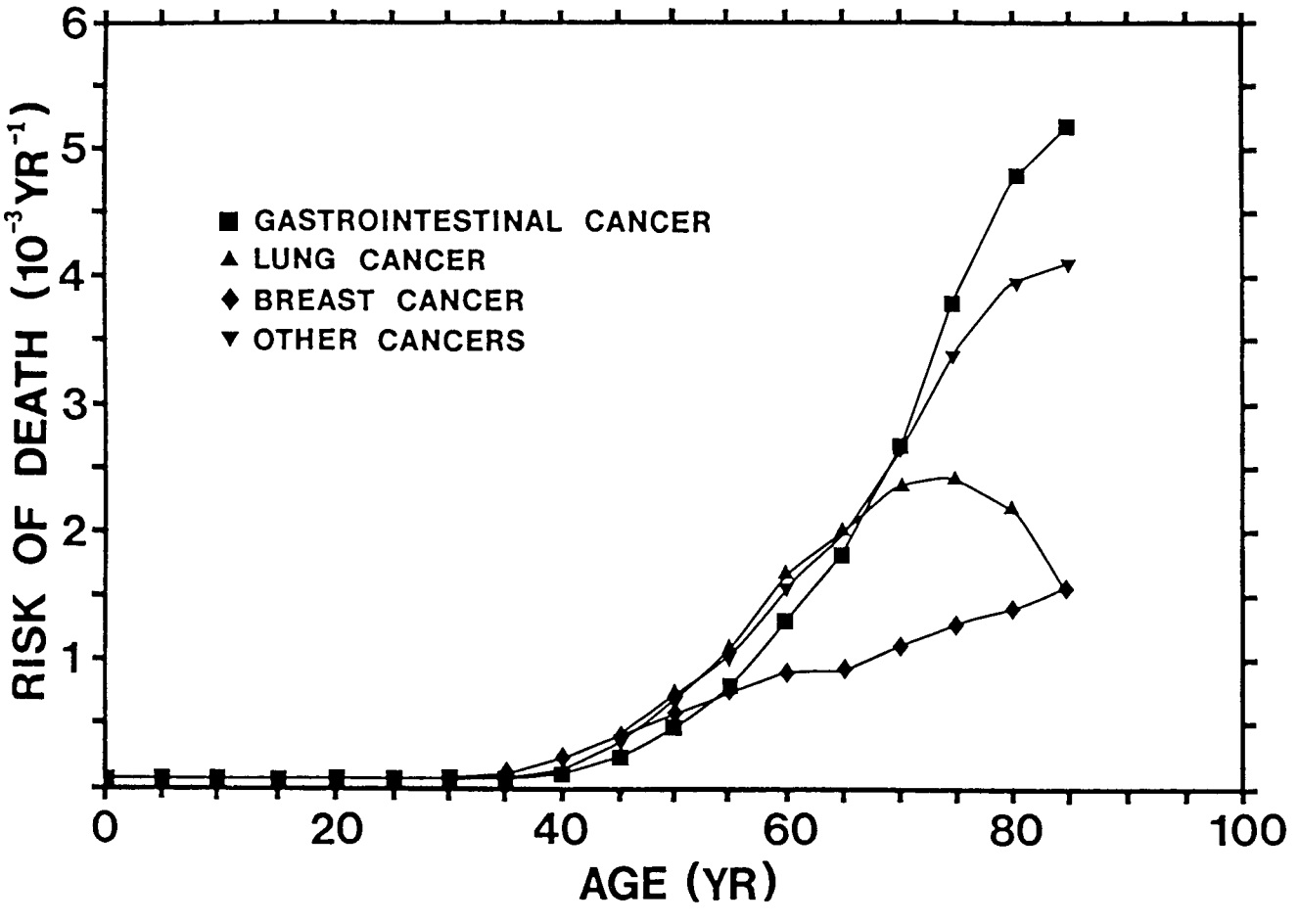

Figure 2.5 Baseline risk of death from four types of cancer (gastrointestinal, lung, breast, and other) as a function of age. Data are from the Vital Statistics of the United States, 1978.

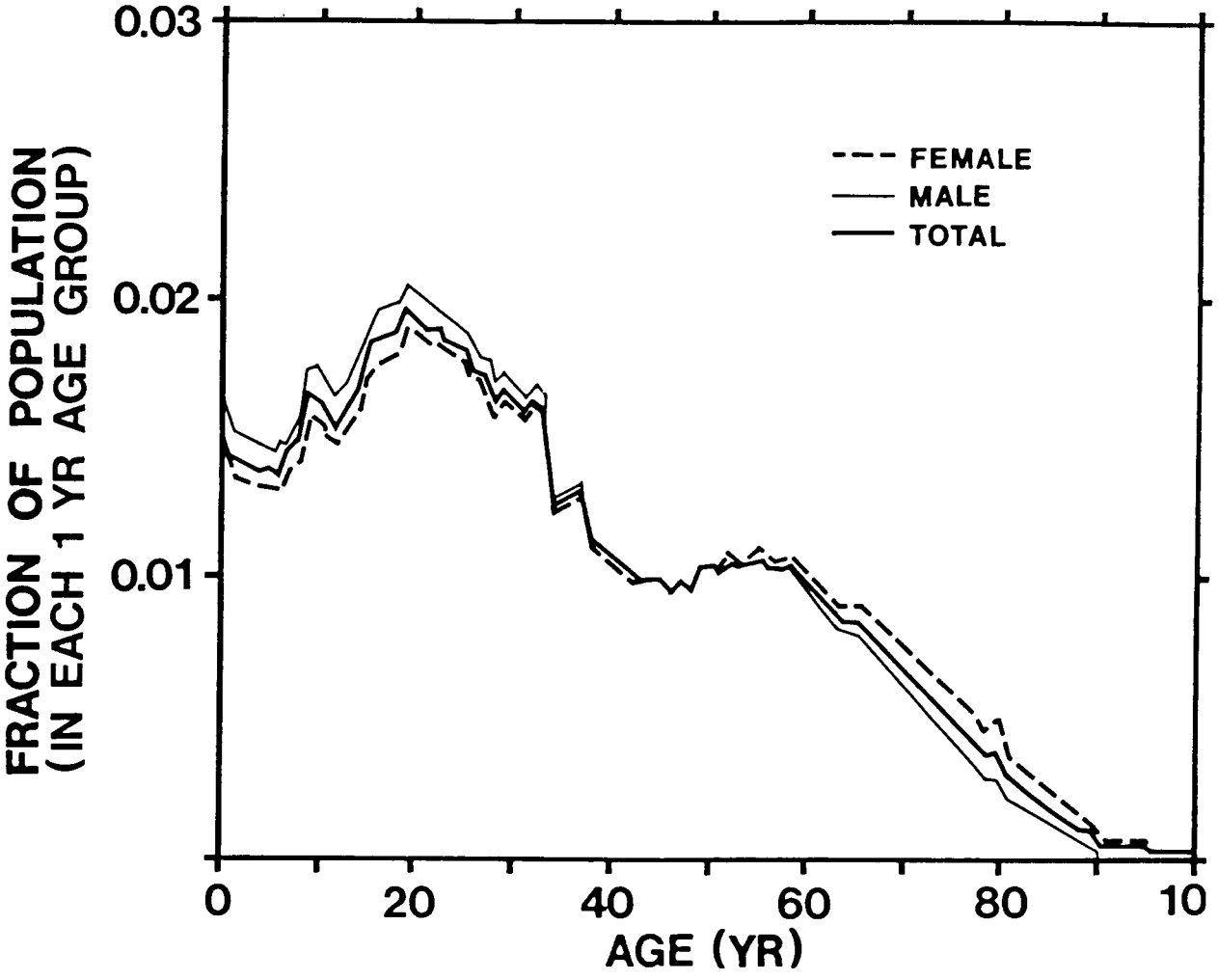

Figure 2.6 Age structure of the U.S. population. Data are from the 1980 Census.

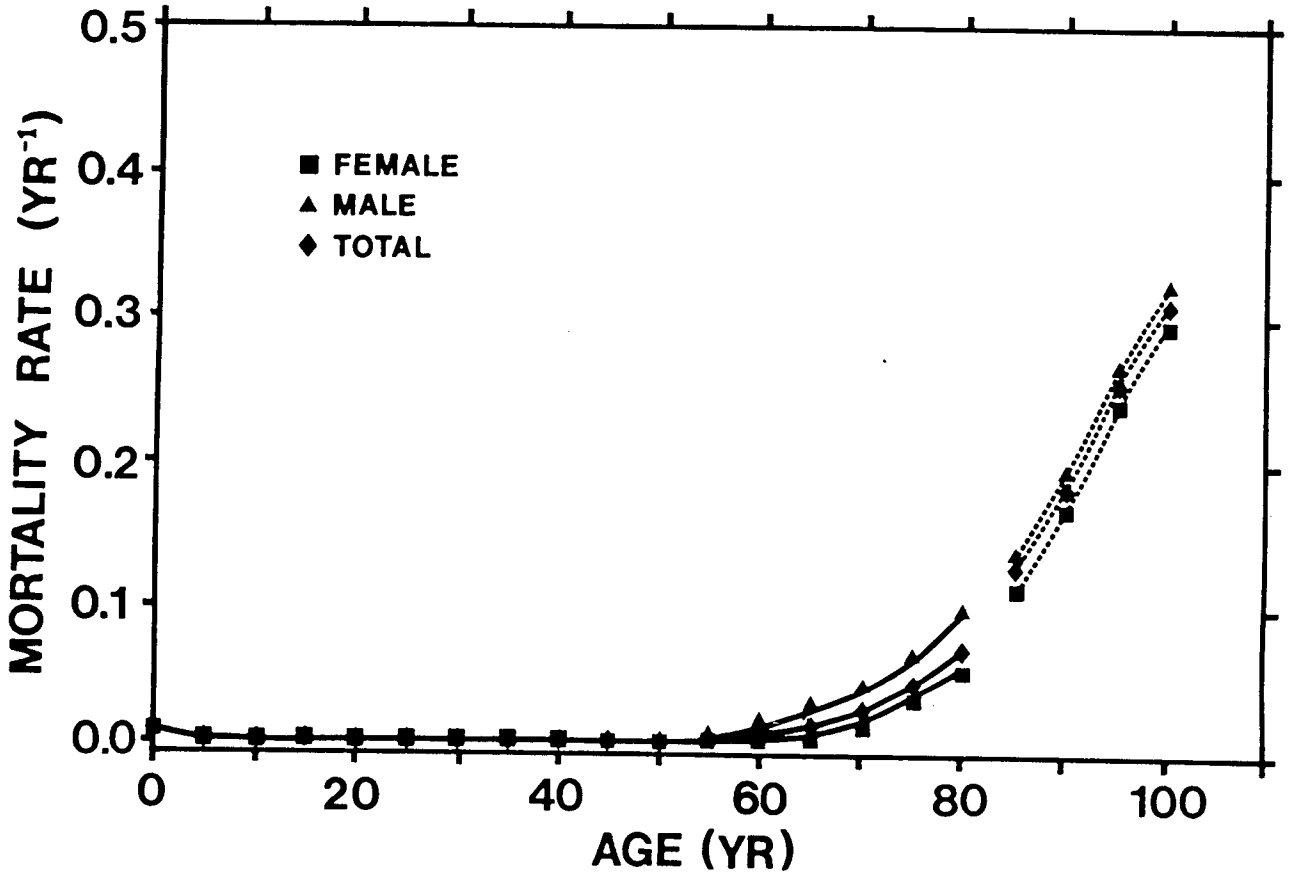

Figure 2.7 Risk of death as a function of age. Data are from the 1978 Life Tables. Dashed sections of the curves were estimated using data from the 1970 Census of the U.S.

specific mortality rates.[10]

The risk in a population is calculated by averaging the risks faced by the various age groups. Specifically, the fraction of a population that would be expected to die τ years after receiving a dose, d, $R(\tau,d)$, is:

$$R(\tau,d) = \sum_k f_k \; s_k(\tau) \; r_k(\tau,d) \tag{2.10}$$

where k indexes the age at exposure; f_k represents the fractions of the populations in each age group at the time of exposure; $s_k(\tau)$ represents the fraction of each age-at-exposure group that will survive other causes of death for τ years; and $r_k(\tau,d)$ is the radiation-induced risk of death τ years after exposure for persons in the kth age group at the time of exposure. To obtain an estimate of the fraction of an exposed population that will eventually die from radiation-induced cancer, R, one evaluates:

$$R(d) = \sum_\tau R(\tau,d) \tag{2.11}$$

Table 2.4 summarizes the results that have been obtained by applying equations (2.10) and (2.11) to the models for central estimates of cancer mortality.[11] The risk in any time period is shown as the product of three factors:

$$R(\tau,d) = R(1) \bullet g(d) \bullet h(\tau) \tag{2.12}$$

where $R(\tau,d)$ is the fraction of the population expected to die from radiation-induced cancer τ years after receiving a dose, d, and the three factors are:

$R(1)$, the lifetime risk due to a dose of 1 Gy;

$g(d)$, a function of dose; and

$h(\tau)$, a function of the time elapsed since receiving the dose.

The values of $h(\tau)$ are simply the fractions of the lifetime risk expected to occur in each time period. The values of $g(d)$ give the ratio of lifetime risks at a dose, d, to risks expected from a dose of 1 Gy.

These risk estimates are appropriate for a population with an age structure similar to that of the 1980 U.S. population. The results are useful for estimation of risks in stationary populations with a stable age structure, such as those that might be exposed only to chronic

[10] Final mortality rates for 1980 were not available at the time this report was being prepared.

[11] These results are simply illustrative. They were derived using the 1980 age-structure of the U.S., the mortality rates for other causes of death from the 1978 U.S. Life Table, and the baseline cancer mortality rates for the U.S. from the 1978 Vital Statistics of the U.S. The same approach could be used with other sources of data to project risks for populations with other characteristics.

Table 2.4 Models for Central Estimates of Late Somatic Mortality

Index (i)	Effect	Dose[a] Rate	Lifetime Risk[b] for a Dose of 1 Gy R(i)	Dose Dependence[c] g(d)	Fraction of Risk Expected In Each Time Interval, h(τ)									
					Time Since Dose, τ (yr)									
					0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
14	leukemia	low	1.44×10^{-3}	d	0.352	0.399	0.249	-	-	-	-	-	-	-
		high	3.70×10^{-3}	$0.39d + 0.61d^2$										
15	bone cancer	low	6.00×10^{-5}	d	0.352	0.399	0.249	-	-	-	-	-	-	-
		high	1.54×10^{-4}	$0.39d + 0.61d^2$										
16	breast cancer[d]	n/a	6.00×10^{-3}	d	-	0.123	0.144	0.165	0.177	0.164	0.125	0.073	0.025	0.004
17	lung cancer	low	2.01×10^{-3}	d	-	0.123	0.141	0.165	0.186	0.177	0.129	0.063	0.015	0.001
		high	5.16×10^{-3}	$0.39d + 0.61d^2$										
18	gastro-intestinal cancer	low	5.67×10^{-3}	d	-	0.110	0.127	0.144	0.165	0.174	0.149	0.094	0.034	0.003
		high	1.46×10^{-2}	$0.39d + 0.61d^2$										
19	thyroid cancer[e]	n/a	5.39×10^{-4}	d	0.105	0.198	0.180	0.160	0.135	0.105	0.070	0.035	0.011	0.001
21	other cancers[f]	low	2.88×10^{-3}	d	-	0.120	0.137	0.154	0.171	0.170	0.137	0.081	0.028	0.002
		high	7.39×10^{-3}	$0.39d + 0.61d^2$										
22	leukemia -*in utero*[g] exposure	n/a	1.20×10^{-4}	d	0.834	0.166	-	-	-	-	-	-	-	-
23	other cancers -*in utero*[g,h] exposure	n/a	1.20×10^{-4}	d	0.909	0.091	-	-	-	-	-	-	-	-

[a] High dose rates are those ≥ 0.05 Gy/day and low dose rates are those < 0.05 Gy/day. The high dose rate model is likely to be important only for dose received within the first several days after an accident from inhalation of radionuclides from the plume and from exposure to external radiation from both the plume and the ground.

[b] This lifetime risks equals the fraction of a cohort with the age-gender-race structure of the 1980 U.S. population that would be expected to die from the stated cause under the age-specific mortality rates for all other causes of death from the 1978 U.S. Life Tables.

[c] Although the dose dependence of risk appears to be different than that given in Table 2.3, it is not. The apparent difference results from the standarization in this table to lifetime risks at a dose of 1 Gy.

[d] These lifetime risk estimates apply to the entire population and represent one half of the risk for females only.

[e] To account for cell killing and eventual ablation of the thyroid, risk calculated for doses > 15 Gy should be modified by the function: $\exp\left[-0.693\left((d-15)/12\right)^2\right]$

[f] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus; but excluding skin and prostate cancer and all other cancers for which disease-specific models have been developed.

[g] These lifetime risk estimates apply to the entire population and represent 1% of the risk for the *in utero* population.

[h] Including all cancers except leukemia.

pathways, e.g., chronic groundshine, ingestion, and/or chronic inhalation of resuspended materials. However, the results are not generally useful for estimating the risks to a population exposed to the plume. Due to natural causes, the number of people in this population will decrease in the years after the accident, and the age structure of the population will change. Therefore, the risks generated by a specific dose will depend upon the time when the dose is received. Tables 2A.1 through 2A.9 in Appendix A of this chapter provide risk estimates for various late somatic effects for each of ten time intervals that are applicable for the population exposed to the plume.[12] Table 2.5 is an example that applies to lung cancer mortality. The tables are abbreviated; they give only the lifetime risk expected at a dose of 1 Gy and the time dependence of the risk. Although the dose-dependence is not shown, it would be the same as that given in Table 2.4. The first row of each table in the series provides risk estimates applicable for the acute dose received from the passing plume and from groundshine. All other rows provide risk estimates applicable for the dose received from chronic pathways.

Morbidity from cancer and benign thyroid nodules may be predicted using similar methods. Tables 2B.1 through 2B.7 in Appendix B of this chapter give results obtained by applying the models and parameters specified in Table 2.3 to a population with the age structure of the 1980 U.S. population. Table 2.6 is an example that applies to lung cancer morbidity. Morbidity estimates for leukemia, bone cancer and cancers from *in utero* exposures have not been provided. Our mortality models for these effects assume that all cases are fatal.[13]

2.2.3 Genetic Effects

In addition to early effects and cancers, an increased incidence of genetic effects would be expected to occur after an accident. Models have been developed for predicting the expected increases in incidence of three categories of genetic disease: single gene effects, chromosomal anomalies, and multifactorial diseases. Because there are differences in the induction and transmission of effects, two models have been developed for single gene effects. One is appropriate for X-linked effects. The other is appropriate for single gene dominant effects. Similarly, the chromosomal anomalies have been divided into two categories: numerical anomalies (aneuploids) and structural anomalies (translocations). Risk estimates for recessive diseases have not been developed.

For single gene effects and chromosomal anomalies, the models that have been developed permit estimation of the time-dependent incidence of radiation-induced genetic disease. The risks may be approximated with equations of the form:

$$r(k,d) = (\alpha d + \beta d^2)\ T^{(k-1)} \qquad (2.13)$$

---

[12] These estimates are simply illustrative. They were derived using the 1980 age-structure of the U.S., the mortality rates for other causes of death from the 1978 U.S. Life Table, and the baseline cancer mortality rates for the U.S. from the 1978 Vital Statistics of the U.S. The same approach could be used with other sources of data to project risks for populations with other characteristics.

[13] As mentioned in Chapter 2 in Volume II, this may result in an overestimation of mortality and an underestimation of morbidity from these effects. However the overall impact of mortality and morbidity from these diseases is not substantially overestimated.

Table 2.5 **Lifetime Lung Cancer Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	5.16×10^{-3} 2.01×10^{-3}	-	0.123	0.141	0.165	0.186	0.177	0.129	0.063	0.015	0.001
10-19		1.77×10^{-3}	-	-	0.160	0.188	0.212	0.202	0.146	0.072	0.018	0.002
20-29		1.48×10^{-3}	-	-	-	0.224	0.253	0.241	0.174	0.085	0.021	0.002
30-39		1.15×10^{-3}	-	-	-	-	0.326	0.310	0.225	0.110	0.027	0.002
40-49		7.74×10^{-4}	-	-	-	-	-	0.460	0.333	0.163	0.040	0.004
50-59		4.20×10^{-4}	-	-	-	-	-	-	0.617	0.302	0.074	0.007
60-69		1.61×10^{-4}	-	-	-	-	-	-	-	0.788	0.193	0.019
70-79		3.42×10^{-5}	-	-	-	-	-	-	-	-	0.912	0.088
80-89		3.00×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2.6 **Lifetime Lung Cancer Morbidity Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	5.70×10^{-3} 2.22×10^{-3}	-	0.125	0.143	0.168	0.188	0.176	0.125	0.059	0.014	0.002
10-19		1.95×10^{-3}	-	-	0.163	0.192	0.215	0.201	0.143	0.067	0.016	0.003
20-29		1.63×10^{-3}	-	-	-	0.229	0.257	0.240	0.171	0.080	0.020	0.003
30-39		1.26×10^{-3}	-	-	-	-	0.334	0.312	0.222	0.104	0.025	0.003
40-49		8.36×10^{-4}	-	-	-	-	-	0.468	0.333	0.157	0.038	0.004
50-59		4.43×10^{-4}	-	-	-	-	-	-	0.626	0.294	0.072	0.008
60-69		1.65×10^{-4}	-	-	-	-	-	-	-	0.788	0.192	0.002
70-79		3.52×10^{-5}	-	-	-	-	-	-	-	-	0.904	0.096
80-89		3.38×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

where $r(k,d)$ is the risk, d is the gonadal dose (Gy), T is the intergenerational transmission rate, k is the number of generations since exposure, and α and β are parameters of the dose-response model.[14] The risk predicted by equation 2.13 is the probability that a child born k generations after an accident will exhibit the genetic effect in question. In Chapter 3 of Volume II, methods are described for predicting risks in great detail based upon demographic methods using age-specific fertility, natality, and mortality data. The models presented here are simplifications, which can be more easily implemented.

Table 2.7 lists the parameters appropriate for obtaining central estimates of risk. Once again, linear-quadratic dose-response models have been used for all effects except chromosomal numerical aberrations (aneuploidy). The quadratic component of risk needs to be evaluated only when doses and dose rates are high (i.e., doses above 0.5 Gy within 24 hours). If doses to the gonads are very high, it may be necessary to account for the probability that the exposed individual will be sterile and therefore unable to transmit any radiation-induced genetic damage.

The approximate distribution of genetic risks over time is illustrated in Figure 2.8. The influence of the intergenerational transmission rate is apparent. Fifty percent of the cumulative incidence of single gene dominant effects, nearly 90% of the chromosomal unbalanced translocations, and all of the aneuploids would be expected to occur within the first three generations after exposure.

The models presented above allow one to estimate the risk of an effect in a child born k generations after an accident. To obtain estimates of the number of effects expected as a function of time, these models must be coupled with simple demographic models. For the prediction of genetic effects, the most important demographic factor is the birth rate. The crude birth rate in the 1980 U.S. population was 0.016 live births/person • year. If this birth rate continues, each person in the population would be expected on the average to give birth to 0.48 children in the characteristic 30-year intergenerational time. Under these simple assumptions, the incidence of genetic defects in the kth generation *per exposed individual* becomes:[15]

$$R(k,d) = 0.48\, r(k,d) \tag{2.14}$$

By summing over all future generations, one obtains $R(d)$, the integrated future incidence of genetic defects expected to occur due to an average dose to the gonads, d.[16] Table 2.8 presents the results obtained by applying (2.14) to the model parameters for individual risks given in Table 2.7. To simplify presentation, the risk in any generation has been expressed as the product of three terms:

---

[14] For most genetic effects, the average dose to the gonads of the ancestors is the basis for risk estimation, i.e., (dose to ovaries + dose to testes)/2. Exceptions are noted.

[15] These models assume population stability. It would be relatively simple to modify them to accomodate approximately exponential population growth or decay.

[16] The sum of the infinite series $(T)^k$, for $0 < T < 1$, is $\dfrac{1}{(1-T)}$.

Table 2.7 Models for Central Estimates of Genetic Effects in Individuals

Index (i)	Effect	Model[a,b] r(k,d)
	Single gene	
25	dominant	$30 \times 10^{-4}(d + d^2)0.8^{k-1}$
26	X-linked	$18 \times 10^{-4}(d + d^2)0.8^{k-1}$
	Chromosome	
27	numerical aberration (aneuploidy)[c]	$10 \times 10^{-4}(d)0^{k-1}$
28	structural aberration (unbalanced translocation)[d]	$13 \times 10^{-4}(d + d^2)0.4^{k-1}$
29	Multifactorial[e]	n/a

[a] Predicts risk that a descendent born k generations after parents received an average dose to the gonads of d (Gy) will exhibit the stated effect.

[b] For doses received at low dose rate the quadratic term is dropped.

[c] This relies on the definitions $0^0 \equiv 1$ and $0^a \equiv 0$ for $a \neq 0$.

[d] For dose of more than 2 Gy received acutely, the risk should be calculated on the basis of a 2 Gy dose.

[e] Risk estimates were not developed for multifactorial diseases in each generation. Time integrated risks are given in Table 2.8.

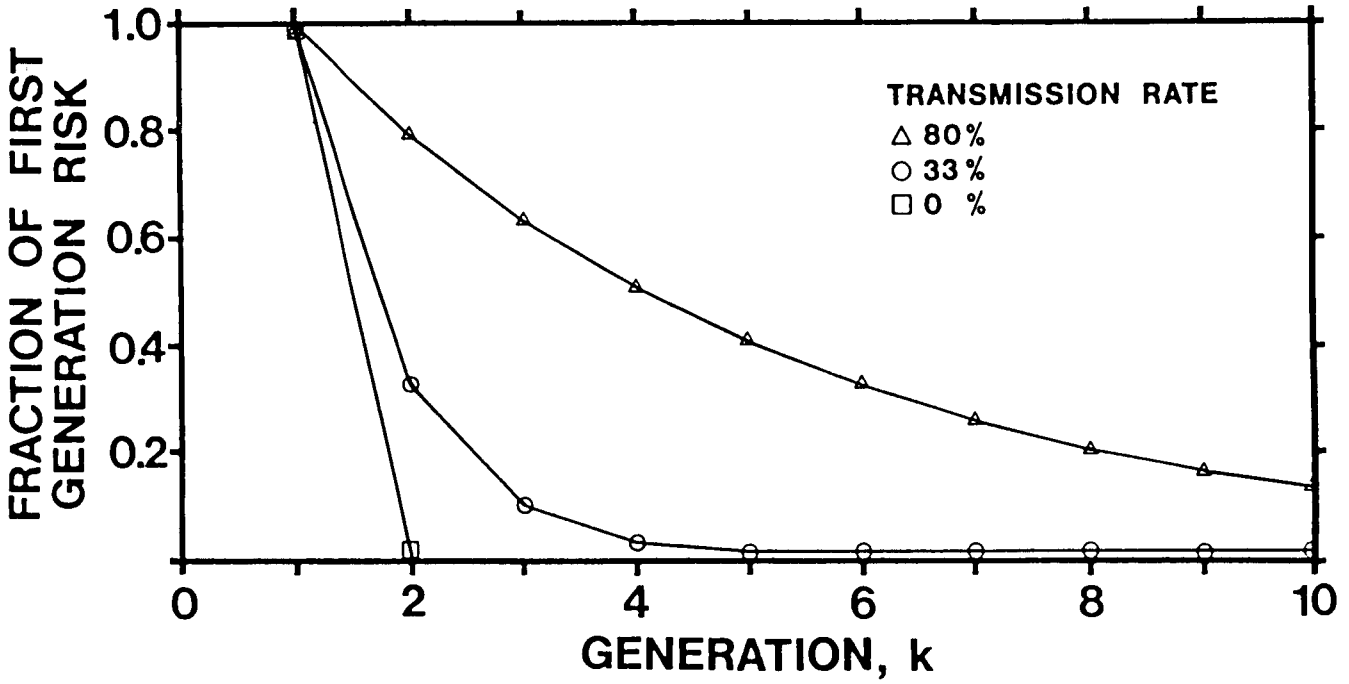

Figure 2.8 Approximate time dependence of genetic risks for various intergenerational transmission rates.

Table 2.8 Models for Central Estimates of Population Genetic Risks

Index (i)	Effect	Dose Rate[a,d]	Integrated Risk for a Dose of 1 Gy R(1)[b]	Dose Dependence g(d)	Fraction of Risk Expected in Each Generation, h(k)					
					Generation, k					
					1	2	3	4	5	>5
	Single Gene									
25	dominant	low	0.72×10^{-2}	d	0.200	0.160	0.128	0.102	0.082	0.328
		high	1.44×10^{-2}	$0.5d + 0.5d^2$						
26	X-linked[c]	low	2.16×10^{-3}	d	0.200	0.160	0.128	0.102	0.082	0.328
		high	4.32×10^{-3}	$0.5d + 0.5d^2$						
	Chromosome Aberrations									
27	numerical (aneuploidy)	n/a	4.80×10^{-4}	d	1.000	0	0	0	0	0
28	structural (unbalanced translocations)	low	1.04×10^{-3}	d	0.600	0.240	0.096	0.038	0.015	0.010
		high	2.08×10^{-3}	$0.5d + 0.5d^2$						
29	Multifactorial	low	0.72×10^{-2}	d	n/a					
		high	1.44×10^{-2}	$0.5d + 0.5d^2$						

[a] Dose rates of more than 0.5 Gy in 24 hours are considered high.

[b] Fraction of a cohort with the 1980 age structure that would be expected to have a descendant in any future generation suffer from a radiation-induced effect at a dose of 1 Gy.

[c] These risk estimates apply to both male and female descendants.

[d] For dose of more than 2 Gy received acutely, the risk should be calculated on the basis of a 2 Gy dose.

$$R(k,d) = R(1) \bullet g(d) \bullet h(k) \qquad \textbf{(2.15)}$$

where $R(k,d)$ is the incidence of radiation-induced genetic defects in the kth generation due to a dose, d, and the three factors are:

$R(1)$, the probability, integrated over all future generations, that a descendent of a member of the exposed cohort will experience a genetic defect due to a dose of 1 Gy;

$g(d)$, a function of dose; and

$h(k)$, a function of the number of generations since the dose.

The values of $h(k)$ are simply the fractions of the integrated future risk expected to occur in each generation. The values of $g(d)$ give the ratio of integrated future risk at a dose, d, to risks expected from a dose of 1 Gy.

The dynamics of inheritance of multifactorial diseases are not well understood. Therefore, an estimate of the cumulative incidence of these diseases is given without any estimate of the distribution of these effects over time.

These risk estimates are appropriate for a population with a stable age structure. They are not strictly appropriate for predicting the risk due to chronic dose received by the population initially exposed to the plume. This population will age, and as time passes will give birth to fewer and fewer children. Therefore the genetic damage transmitted by this population to future generations will become smaller and smaller as the interval between the time of the accident and the receipt of the dose increases. As a first approximation, an appropriate correction is found by considering the decrease in birth rate with time in this population. Values of the correction term, $c(\tau)$, for various times since the accident are given in Table 2.9.

Genetic effects are influenced by the amount of genetic damage within the entire population of potential parents. Therefore, the distribution of doses within this population is a key determinant of the likelihood of effects. If the doses to all individuals in this population are low or are received at low dose rate, the quadratic term drops out of the dose-response model and the risk is determined solely by the average dose to the population:

$$r(k,\bar{d}) = (\alpha \bar{d})\ T^{(k-1)} \qquad (2.16)$$

where $r(k,\bar{d})$ is the risk, and $\bar{d}$ is the average dose to the testes and ovaries.[17] If, on the other hand, some members of the population receive high doses at high dose rate, then the risk in the population must be determined by averaging the individual risks:

[17] To be explicit, $\bar{d} \approx 0.5\ \bar{d}_m + 0.5\ \bar{d}_f$ where $\bar{d}_m$ is the average dose to the testes of males in the population, and $\bar{d}_f$ is the average dose to the ovaries of females in the population.

Table 2.9 Correction Factors for Genetic Risk Due to Chronic Dose in the Population Initially Exposed to the Plume

Time Since Accident τ (yr)	Correction Factor $c(\tau)$
1 - 10	1.00
11 - 20	1.00
21 - 30	0.86
31 - 40	0.19
41 - 50	0.01
>50	0.00

$$r(k) = \left[\alpha\left(\sum_p f_p\, d_p\right) + \beta\left(\sum_p f_p\, d_p^2\right)\right] T^{(k-1)} \qquad \textbf{(2.17)}$$

where d_p is the average dose to the gonads of the pth subgroup of the population, and f_p is the fraction of the total population in the pth subgroup.

A wide array of effects is possible within each category of genetic disease. Some effects lead to premature death. Others are responsible for disability, but are not lethal. The models given above reflect incidence. In Chapter 3 of Volume II, information is provided on the fraction of cases of each class of effect that is fatal, the typical reduction of life expectancy, and the duration and severity of symptoms.

2.2.4 Influence of Early Mortality on Risks of Early Morbidity, Somatic, and Genetic Effects

Estimates of risks of early morbidity and late somatic and genetic effects must be adjusted to reflect early mortality. The adjustments to early morbidity and somatic risks can be made using:

$$R_a = R\ e^{-(H_1 + H_2 + H_3)} \qquad (2.18)$$

where R_a represents the adjusted risk of early morbidity or somatic effects, R is the unadjusted risk, and $e^{-(H_1 + H_2 + H_3)}$ is the probability of surviving the three causes of early death, where H_1, H_2, and H_3 are the cumulative hazards for hematopoietic, pulmonary, and gastrointestinal syndromes, respectively. Estimates of early morbidity adjusted in this way reflect the risks in survivors, and are most appropriate for effects such as skin burns, sterility, and cataracts. Effects such as vomiting, nausea, and fatigue could presage death and be experienced by both those who survive and those who die. This simple calculation is appropriate because the early deaths do not influence the age distribution of the population.[18] For early morbidity and somatic effects this adjustment must be performed on a geographic cell-specific basis.

Similarly, the risk of developing microcephaly, mental retardation, leukemia *in utero*, and other cancers *in utero* should be adjusted to reflect the probability of early death due to pre- or neonatal exposure.

Genetic risks are determined by the distribution of doses in the pool of potential parents. Because individuals choose mates without regard to the geographic boundaries of model cells, the doses received within specific geographic cells are important only through their influence on the distribution of doses in this pool. Because of this, it is appropriate to adjust the distribution of doses.

In a geographic cell with N_m males and N_f females, the average dose to the gonads of nonsterile survivors would be:

---

[18] Actually, the correction required is somewhat more complex to account for the varying degrees of care received: $R_a = R\left[f_m e^{-(H_{1m} + H_2 + H_3)} + f_s e^{-(H_{1s} + H_2 + H_3)} + f_i e^{-(H_{1i} + H_2 + H_3)}\right]$ where the subscripts m, s, and i refer to the type of care received, and f represents the fraction of the population receiving it.

$$\bar{d} = \frac{n_m\, d_m + n_f\, d_f}{n_m + n_f} \tag{2.19}$$

where d_m is the dose to the testes, d_f is the dose to the ovaries, n_m is the number of nonsterile male survivors, and n_f is the number of nonsterile female survivors, calculated using:

$$n_m = N_m\, e^{-\left(H_1 + H_2 + H_3 + H_{11_m}\right)} \tag{2.20}$$

$$n_f = N_f\, e^{-\left(H_1 + H_2 + H_3 + H_{11_f}\right)} \tag{2.21}$$

where H_1 is the cumulative hematopoietic hazard, H_2 is the cumulative pulmonary hazard, H_3 is the cumulative gastrointestinal hazard, H_{11_m} is the cumulative hazard for sterility in males, and H_{11_f} is the cumulative hazard for sterility in females.

It is conceivable that early pre- and neonatal deaths could influence the age structure and birth rate in the population and thus have a secondary effect on genetic risks. This would not be expected to be a substantial effect, because of the geographic extent of the pool of potential parents, and is ignored in our models.

2.3 Models for Upper and Lower Estimates

Because the exact dose-response functions for radiation-induced health effects are not known, the Working Groups provided models for deriving upper, central, and lower estimates of risk. The models for upper and lower estimates are summarized here. The interpretation of these upper and lower estimates is discussed in Chapter 1 of this volume.

For early and continuing effects, the upper and lower estimates have been derived using identical models to those used for central estimates. Only the parameters differ. Because death is more significant than illness, and because most early deaths in the aftermath of a nuclear power plant accident are expected to be caused by injury of the bone marrow, the Early Effects Working Group concentrated on analysis of the uncertainty in estimating the risk of death from hematopoietic syndrome. Based upon a reanalysis of several sources of data, they concluded that there is approximately 20% uncertainty in the value of the LD_{50} (or α) for this effect, and about 50% uncertainty in the shape parameter (or β). However, because estimates of the shape parameter and the LD_{50} tend to be negatively correlated, the Working Group recommended that to derive upper estimates of risk, low values of the LD_{50} be used in conjunction with high values of the shape parameter. Similarly, they recommended that to derive lower estimates of risk, high values of the LD_{50} be used in conjunction with low values of the shape parameter. The parameters needed for calculating upper and lower estimates are summarized in Table 2.10.

For late somatic effects, the upper and lower estimates were derived in some cases using different models from those used to obtain central estimates. In other cases, the same models were used with modified parameters. For benign thyroid nodules models for upper and lower estimates have not been developed. For thyroid cancer the only difference in the upper,

Table 2.10 Models for Upper and Lower Estimates for Early and Continuing Effects

Index (i)	Effect	Parameters Required for [a,b]			
		Lower Estimates		Upper Estimates	
		α_{i1}	β	α_{i1}	β
1	Hematopoietic Syndrome				
	minimal treatment	4.0	6.6	2.8	15
	supportive treatment	6.0	4.4	3.4	10
2	Pulmonary Syndrome				
	minimal treatment	[9.6]	[2.0]	[6.6]	[4.5]
3	Gastrointestinal Syndrome	[18]	[6.6]	[12.5]	[15]
4	Pre- and Neonatal Deaths[c]	[1.2]	[2.0]	[0.8]	[4.5]

[a]Parameter values given here are appropriate for the dose received within 1 day of an accident.

[b]The parameter estimates given in brackets were derived on the assumption that the uncertainty for pulmonary syndrome, gastrointestinal syndrome, and pre- and neonatal deaths is the same as the uncertainty for the hematopoietic syndrome.

[c]The parameters given here represent a weighted average of the response of pre- and neonates in various stages of development.

lower, and central estimates is the treatment of internal dose from ^{131}I. In the central estimate, ^{131}I is assigned 1/3 the effectiveness of external dose. In the lower estimate, ^{131}I is assigned 1/10 effectiveness of external dose; and in the upper estimate dose from ^{131}I is assumed to be equivalent to external dose. For the other effects there are differences in the risk coefficients, the model for dose-dependence, and/or the model for risk projection. For example, the central estimate for breast cancer is based on a relative risk model with a risk coefficient of 45% per Gy and a linear dose-response function. The lower estimate of breast cancer is derived using an absolute risk model and a linear-quadratic dose-response function, and the upper estimate is derived using a relative risk model with age-at-exposure-specific risk coefficients of 103% per Gy for those under 20 years old and 42% per Gy for those over 20. The models and parameter values recommended for obtaining upper and lower estimates of these risks are summarized in Table 2.11.

The model used affects not only the integrated risk, but also the distribution of mortality risks over time. In the case of four cancers (breast, lung, gastrointestinal, and "other"), the lower or upper estimates were estimated using different risk projection models than those used for central estimates. The distribution of mortality risks over time for the lower and upper estimates of these effects are summarized in Appendix A of this chapter (Tables 2A.10 - 2A.15). The distribution of morbidity risks over time for the lower and upper estimates of these effects are summarized in Appendix B of this chapter (Tables 2B.8 - 2B.13).

For genetic effects, the major source of uncertainty is apparently in estimating gametic induction rates. The parameters needed to obtain lower and upper estimates are summarized in Table 2.12.

Table 2.11a Models for Lower Estimates of Somatic Risks for Individuals

Index	Effect	Type of Model	Latency	Plateau	Minimum Age	Coefficient		α	β
						Mortality	Morbidity		
14	Leukemia	Absolute, linear - quadratic	2	25	n/a	2.24×10^{-4}	n/a	0.1	0.6
15	Bone cancer	Absolute, linear - quadratic	2	25	n/a	1.00×10^{-5}	n/a	0.1	0.6
16	Breast cancer	Absolute, linear - quadratic, non-age-specific	10	∞	30	2.60×10^{-4}	7.4×10^{-4}	0.1	0.6
17	Lung cancer	Absolute, linear - quadratic	10	∞	40	2.00×10^{-4}	2.2×10^{-4}	0.1	0.6
18	Gastrointestinal cancer	Absolute, linear - quadratic	10	∞	n/a	2.70×10^{-4}	4.6×10^{-4}	0.1	0.6
20	Skin cancer	Absolute, linear-quadratic	10	∞	n/a	n/a	2.00×10^{-4}	0.1	0.6
21	Other cancers	Absolute, linear - quadratic	10	∞	n/a	1.50×10^{-4}	2.9×10^{-4}	0.1	0.6
22	In utero - leukemia	Absolute, linear	0	12	n/a	2.50×10^{-3}	n/a	0.4	0
23	In utero - other	Absolute, linear	0	10	n/a	2.80×10^{-3}	n/a	0.4	0

Table 2.11b Models for Upper Estimates of Somatic Risks for Individuals

Index	Effect	Type of Model	Latency	Plateau	Minimum Age	Coefficient		α	β
						Mortality	Morbidity		
14	Leukemia	Absolute, linear	2	25	n/a	2.24×10^{-4}	n/a	1.0	0
15	Bone cancer	Absolute, linear	2	25	n/a	1.00×10^{-5}	n/a	1.0	0
16	Breast cancer	Relative, linear age-specific							
		$a_e < 20$	10	∞	30	103%	103%	1.0	0
		$a_e \geq 20$	10	∞	30	42%	42%	1.0	0
17	Lung cancer	Relative, linear	10	∞	40	37%	37%	1.0	0
18	Gastrointestinal cancer	Relative, linear	10	∞	n/a	39%	39%	1.0	0
20	Skin Cancer	Absolute, linear	10	∞	n/a	n/a	2.0×10^{-4}	1.0	0
21	Other cancer	Relative, linear	10	∞	n/a	20%	20%	1.0	0

Table 2.12 Models for Lower and Upper Estimates for Genetic Risks in Individuals

Index (i)	Effect	Model for Risk [a,b]	
		Lower Estimate	Upper Estimate
	Single gene		
24	dominant	$5 \times 10^{-4}(d_m + d^2_m)0.8^{k-1}$	$90 \times 10^{-4}(d + d^2)0.8^{k-1}$
25	**X-linked**	$2.88 \times 10^{-4}(d_m + d^2_m)0.8^{k-2}$	$72 \times 10^{-4}(d + d^2)0.8^{k-1}$
	Chromosome		
26	**numerical aberrations (aneuploidy)**	0	$30 \times 10^{-4}(d)0^{k-1}$
27	**structural aberrations (unbalanced translocations)**	$0.8 \times 10^{-4}(d_m + d^2_m)0.4^{k-1}$	$32.5 \times 10^{-4}(d + d^2)0.4^{k-1}$
28	**Multifactorial[c]**	n/a	

[a] Predicts risk that a descendent born k generations after parents received an average dose to the gonads of d (Gy) will exhibit the stated effect.

[b] For doses received at low dose rate the quadratic term is dropped.

[c] Risk estimates were not developed for multifactorial diseases in each generation. However the lower estimate time integrated risk model is:

$R = 0.46 \times 10^{-2} (d_m + d^2_m)$

and the upper estimate time integrated risk model is:

$R = 9.12 \times 10^{-2} (d + d^2)$.

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Appendix 2A

CANCER MORTALITY TABLES FOR THOSE EXPOSED TO THE PLUME

NOTE: These tables are abbreviated. They do not give the dose-dependence of risk. For central estimates (Tables 2A.1-2A.9) the dose-dependence would be the same as that shown in Table 2.4 in the body of the text. For lower estimates of all cancers (Tables 2A.10-2A.13) at low dose rate, risk is proportional to dose. For lower estimates of breast, lung, gastrointestinal, and "other" cancers at high dose rate, risk is proportional to $0.14\ d + 0.86\ d^2$. For upper estimates of all cancers (Tables 2A.14-2A.15) risk is proportional to dose.

Table 2A.1 Lifetime Leukemia Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	3.70×10^{-3}	0.352	0.399	0.249	-	-	-	-	-	-	-
	Low	1.44×10^{-3}										
10-19		1.26×10^{-3}	-	0.359	0.399	0.242	-	-	-	-	-	-
20-29		1.07×10^{-3}	-	-	0.373	0.398	0.229	-	-	-	-	-
30-39		8.60×10^{-4}	-	-	-	0.392	0.397	0.211	-	-	-	-
40-49		6.30×10^{-4}	-	-	-	-	0.426	0.393	0.181	-	-	-
50-59		4.01×10^{-4}	-	-	-	-	-	0.482	0.380	0.138	-	-
60-69		2.07×10^{-4}	-	-	-	-	-	-	0.562	0.348	0.090	-
70-79		7.86×10^{-5}	-	-	-	-	-	-	-	0.694	0.276	0.030
80-89		1.82×10^{-5}	-	-	-	-	-	-	-	-	0.859	0.141
90-99		1.71×10^{-6}	-	-	-	-	-	-	-	-	-	1.000

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.2 Lifetime Bone Cancer Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	1.54×10^{-4}	0.352	0.399	0.249	-	-	-	-	-	-	-
	Low	6.00×10^{-5}										
10-19		5.64×10^{-5}	-	0.359	0.399	0.242	-	-	-	-	-	-
20-29		4.78×10^{-5}	-	-	0.373	0.398	0.229	-	-	-	-	-
30-39		3.84×10^{-5}	-	-	-	0.392	0.397	0.211	-	-	-	-
40-49		2.81×10^{-5}	-	-	-	-	0.426	0.393	0.181	-	-	-
50-59		1.79×10^{-5}	-	-	-	-	-	0.482	0.380	0.138	-	-
60-69		9.26×10^{-6}	-	-	-	-	-	-	0.562	0.348	0.090	-
70-79		3.50×10^{-6}	-	-	-	-	-	-	-	0.694	0.276	0.030
80-89		8.09×10^{-7}	-	-	-	-	-	-	-	-	0.859	0.141
90-99		1.17×10^{-7}	-	-	-	-	-	-	-	-	-	1.000

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.3 Lifetime Breast Cancer[a] Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	6.00×10^{-3}	-	0.123	0.144	0.165	0.177	0.164	0.125	0.073	0.025	0.004
10-19	5.28×10^{-3}	-	-	0.165	0.188	0.202	0.188	0.143	0.083	0.028	0.003
20-29	4.42×10^{-3}	-	-	-	0.225	0.242	0.224	0.171	0.100	0.034	0.004
30-39	3.42×10^{-3}	-	-	-	-	0.312	0.290	0.220	0.129	0.044	0.005
40-49	2.35×10^{-3}	-	-	-	-	-	0.421	0.321	0.187	0.064	0.007
50-59	1.36×10^{-3}	-	-	-	-	-	-	0.554	0.323	0.110	0.013
60-69	6.06×10^{-4}	-	-	-	-	-	-	-	0.725	0.246	0.029
70-79	1.68×10^{-4}	-	-	-	-	-	-	-	-	0.896	0.104
80-89	1.75×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

[a] These lifetime risks apply to the entire population and represent one half the risk for females only.

Table 2A.4 Lifetime Lung Cancer Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	5.16×10^{-3}	-	0.123	0.141	0.165	0.186	0.177	0.129	0.063	0.015	0.001
	Low	2.01×10^{-3}										
10-19		1.77×10^{-3}	-	-	0.160	0.188	0.212	0.202	0.146	0.072	0.018	0.002
20-29		1.48×10^{-3}	-	-	-	0.224	0.253	0.241	0.174	0.085	0.021	0.002
30-39		1.15×10^{-3}	-	-	-	-	0.326	0.310	0.225	0.110	0.027	0.002
40-49		7.74×10^{-4}	-	-	-	-	-	0.460	0.333	0.163	0.040	0.004
50-59		4.20×10^{-4}	-	-	-	-	-	-	0.617	0.302	0.074	0.007
60-69		1.61×10^{-4}	-	-	-	-	-	-	-	0.788	0.193	0.019
70-79		3.42×10^{-5}	-	-	-	-	-	-	-	-	0.912	0.088
80-89		3.00×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.5 **Lifetime Gastrointestinal Cancer Mortality (Central Estimate) Risk as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals**

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	1.46×10^{-2}	-	0.110	0.127	0.144	0.165	0.174	0.149	0.094	0.034	0.003
	Low	5.68×10^{-3}										
10-19		4.86×10^{-3}	-	-	0.142	0.162	0.185	0.195	0.167	0.105	0.038	0.006
20-29		4.16×10^{-3}	-	-	-	0.189	0.216	0.228	0.195	0.123	0.045	0.004
30-39		3.38×10^{-3}	-	-	-	-	0.267	0.281	0.240	0.151	0.055	0.006
40-49		2.47×10^{-3}	-	-	-	-	-	0.383	0.327	0.206	0.075	0.009
50-59		1.53×10^{-3}	-	-	-	-	-	-	0.530	0.334	0.122	0.014
60-69		7.20×10^{-4}	-	-	-	-	-	-	-	0.709	0.259	0.032
70-79		2.09×10^{-4}	-	-	-	-	-	-	-	-	0.892	0.108
80-89		2.26×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.6 **Lifetime Thyroid Cancer Mortality Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	5.54×10^{-4}	0.105	0.198	0.180	0.160	0.135	0.105	0.070	0.035	0.011	0.001
10-19	4.26×10^{-4}	-	0.122	0.227	0.201	0.170	0.133	0.088	0.044	0.013	0.002
20-29	3.23×10^{-4}	-	-	0.145	0.264	0.224	0.174	0.115	0.058	0.018	0.002
30-39	2.32×10^{-4}	-	-	-	0.178	0.312	0.242	0.161	0.080	0.024	0.003
40-49	1.54×10^{-4}	-	-	-	-	0.225	0.368	0.244	0.122	0.037	0.004
50-59	8.98×10^{-5}	-	-	-	-	-	0.294	0.423	0.211	0.064	0.008
60-69	4.28×10^{-5}	-	-	-	-	-	-	0.393	0.453	0.138	0.016
70-79	1.46×10^{-5}	-	-	-	-	-	-	-	0.532	0.419	0.049
80-89	2.59×10^{-6}	-	-	-	-	-	-	-	-	0.722	0.278
90-99	1.54×10^{-7}	-	-	-	-	-	-	-	-	-	1.000

Table 2A.7 Lifetime Mortality Risk for "Other" Cancers[a] (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	7.39×10^{-3}	-	0.120	0.137	0.154	0.171	0.170	0.137	0.081	0.028	0.002
	Low	2.87×10^{-3}										
10-19		2.47×10^{-3}	-	-	0.155	0.175	0.194	0.193	0.155	0.092	0.032	0.004
20-29		2.09×10^{-3}	-	-	-	0.207	0.230	0.229	0.184	0.109	0.037	0.004
30-39		1.66×10^{-3}	-	-	-	-	0.290	0.289	0.232	0.137	0.047	0.005
40-49		1.18×10^{-3}	-	-	-	-	-	0.406	0.326	0.193	0.066	0.009
50-59		6.96×10^{-4}	-	-	-	-	-	-	0.550	0.325	0.112	0.013
60-69		3.15×10^{-4}	-	-	-	-	-	-	-	0.722	0.248	0.030
70-79		8.71×10^{-5}	-	-	-	-	-	-	-	-	0.894	0.106
80-89		9.30×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus, but excluding skin and prostate cancer and all cancers for which disease specific risk models have been developed.

[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.8 Lifetime Mortality Risk for <u>In Utero</u> Leukemia[a] (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	1.20×10^{-4}	0.834	0.166	-	-	-	-	-	-	-	-
10-19	1.17×10^{-4}	-	0.834	0.166	-	-	-	-	-	-	-
20-29	1.16×10^{-4}	-	-	0.835	0.165	-	-	-	-	-	-
30-39	1.14×10^{-4}	-	-	-	0.835	0.165	-	-	-	-	-
40-49	1.11×10^{-4}	-	-	-	-	0.839	0.161	-	-	-	-
50-59	1.04×10^{-4}	-	-	-	-	-	0.846	0.154	-	-	-
60-69	8.80×10^{-5}	-	-	-	-	-	-	0.860	0.140	-	-
70-79	6.16×10^{-5}	-	-	-	-	-	-	-	0.892	0.108	-
80-89	2.72×10^{-5}	-	-	-	-	-	-	-	-	0.949	0.051
90-99	6.60×10^{-6}	-	-	-	-	-	-	-	-	-	1.000

[a] These lifetime risks apply to the entire population and represent one percent of the risk for the <u>in utero</u> population.

Table 2A.9 Lifetime Mortality Risk for *In Utero* "Other" Cancers[a,b] (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	1.20×10^{-4}	0.909	0.091	-	-	-	-	-	-	-	-
10-19	1.19×10^{-4}	-	0.910	0.090	-	-	-	-	-	-	-
20-29	1.19×10^{-4}	-	-	0.910	0.090	-	-	-	-	-	-
30-39	1.18×10^{-4}	-	-	-	0.910	0.090	-	-	-	-	-
40-49	1.14×10^{-4}	-	-	-	-	0.912	0.088	-	-	-	-
50-59	1.07×10^{-4}	-	-	-	-	-	0.916	0.084	-	-	-
60-69	9.16×10^{-5}	-	-	-	-	-	-	0.925	0.075	-	-
70-79	6.52×10^{-5}	-	-	-	-	-	-	-	0.943	0.057	-
80-89	2.96×10^{-5}	-	-	-	-	-	-	-	-	0.973	0.027
90-99	7.40×10^{-6}	-	-	-	-	-	-	-	-	-	1.000

[a] These lifetime risk estimates apply to the entire population and represent one percent of the risk for the *in utero* population.

Table 2A.10 **Lifetime Breast Cancer[a] Mortality Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fraction of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	3.01×10^{-3}	-	0.163	0.194	0.201	0.170	0.129	0.084	0.043	0.013	0.003
	Low	4.30×10^{-4}										
10-19		3.66×10^{-4}	-	-	0.231	0.240	0.204	0.155	0.101	0.051	0.016	0.002
20-29		2.81×10^{-4}	-	-	-	0.313	0.265	0.201	0.132	0.066	0.020	0.003
30-39		1.93×10^{-4}	-	-	-	-	0.386	0.293	0.191	0.096	0.029	0.005
40-49		1.19×10^{-4}	-	-	-	-	-	0.477	0.312	0.157	0.048	0.006
50-59		6.20×10^{-5}	-	-	-	-	-	-	0.596	0.301	0.097	0.006
60-69		2.50×10^{-5}	-	-	-	-	-	-	-	0.746	0.228	0.026
70-79		6.36×10^{-6}	-	-	-	-	-	-	-	-	0.898	0.102
80-89		6.43×10^{-7}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] These lifetime risks apply to the entire population and represent one half the risk for females only.

[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.11 **Lifetime Lung Cancer Mortality Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	3.71×10^{-3}	-	0.159	0.188	0.202	0.184	0.133	0.082	0.039	0.012	0.001
	Low	5.30×10^{-4}										
10-19		4.67×10^{-4}	-	-	0.223	0.240	0.218	0.158	0.098	0.046	0.014	0.003
20-29		3.61×10^{-4}	-	-	-	0.309	0.281	0.204	0.125	0.059	0.018	0.004
30-39		2.50×10^{-4}	-	-	-	-	0.407	0.295	0.182	0.086	0.026	0.004
40-49		1.49×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		7.41×10^{-5}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		2.87×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0.026
70-79		7.21×10^{-6}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		7.57×10^{-7}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.12 Lifetime Gastrointestinal Cancer Mortality Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	6.37×10^{-3} 9.10×10^{-4}	-	0.244	0.215	0.182	0.146	0.106	0.065	0.031	0.009	0.002
10-19		7.11×10^{-4}	-	-	0.285	0.241	0.193	0.140	0.086	0.041	0.012	0.002
20-29		5.10×10^{-4}	-	-	-	0.337	0.270	0.196	0.121	0.057	0.017	0.002
30-39		3.37×10^{-4}	-	-	-	-	0.407	0.296	0.182	0.086	0.026	0.003
40-49		1.99×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		1.00×10^{-4}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		3.89×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0.026
70-79		9.33×10^{-6}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		1.03×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.13 Lifetime Mortality Risk for "Other" Cancers[a] (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	3.50×10^{-3} 5.00×10^{-4}	-	0.244	0.215	0.182	0.146	0.106	0.065	0.031	0.009	0.002
10-19		3.96×10^{-4}	-	-	0.285	0.241	0.193	0.140	0.086	0.041	0.012	0.002
20-29		2.83×10^{-4}	-	-	-	0.337	0.270	0.196	0.121	0.057	0.017	0.002
30-39		1.87×10^{-4}	-	-	-	-	0.407	0.296	0.182	0.086	0.026	0.003
40-49		1.11×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		5.56×10^{-5}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		2.16×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0 026
70-79		5.41×10^{-6}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		5.70×10^{-7}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus; but excluding skin and prostate cancer and all other cancers for which disease specific risk models have been developed.

[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2A.14 **Lifetime Breast Cancer[a] Mortality Risk (Upper Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	8.70×10^{-3}	-	0.080	0.100	0.136	0.177	0.188	0.164	0.110	0.040	0.005
10-19	7.90×10^{-3}	-	-	0.109	0.148	0.192	0.204	0.179	0.120	0.043	0.005
20-29	7.04×10^{-3}	-	-	-	0.166	0.215	0.229	0.201	0.134	0.048	0.007
30-39	5.86×10^{-3}	-	-	-	-	0.258	0.274	0.241	0.161	0.058	0.008
40-49	4.35×10^{-3}	-	-	-	-	-	0.371	0.325	0.217	0.078	0.009
50-59	2.74×10^{-3}	-	-	-	-	-	-	0.516	0.345	0.124	0.015
60-69	1.33×10^{-3}	-	-	-	-	-	-	-	0.713	0.257	0.030
70-79	3.80×10^{-4}	-	-	-	-	-	-	-	-	0.894	0.106
80-89	4.00×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

[a]These lifetime risks apply to the entire population and represent one half the risk for females only.

Table 2A.15 **Lifetime Lung Cancer Mortality Risk (Upper Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	1.38×10^{-2}	-	0.123	0.141	0.165	0.186	0.177	0.129	0.063	0.015	0.001
10-19	1.21×10^{-2}	-	-	0.160	0.188	0.212	0.202	0.146	0.072	0.018	0.002
20-29	1.02×10^{-2}	-	-	-	0.224	0.253	0.241	0.174	0.085	0.021	0.002
30-39	7.89×10^{-3}	-	-	-	-	0.326	0.310	0.225	0.109	0.027	0.003
40-49	5.32×10^{-3}	-	-	-	-	-	0.460	0.333	0.163	0.039	0.005
50-59	2.88×10^{-3}	-	-	-	-	-	-	0.617	0.302	0.074	0.007
60-69	1.10×10^{-3}	-	-	-	-	-	-	-	0.788	0.193	0.019
70-79	2.33×10^{-4}	-	-	-	-	-	-	-	-	0.912	0.088
80-89	2.06×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

Appendix 2B

CANCER INCIDENCE TABLES FOR THOSE EXPOSED TO THE PLUME

NOTE: These tables are abbreviated. They do not give the dose-dependence of risk. For central estimates of morbidity (Tables 2B.1-2B.7) the dose-dependence would be the same as that shown for mortality in Table 2.4 in the body of the text. For central estimates of skin cancer morbidity, risk is proportional to $0.39\ d + 0.61\ d^2$. For central estimates of benign thyroid nodules, risk is proportional to dose. For lower estimates of all cancers (Tables 2B.8-2B.11) at low dose rate, risk is proportional to dose. For lower estimates of breast, lung, gastrointestinal, and "other" cancers at high dose rate, risk is proportional to $0.14\ d + 0.86\ d^2$. For upper estimates of all cancers (Tables 2B.12-2B.13) risk is proportional to dose.

Table 2B.1 Lifetime Breast Cancer[a] Morbidity Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	1.72×10^{-2}	-	0.133	0.155	0.176	0.179	0.157	0.115	0.063	0.021	0.001
10-19	1.53×10^{-2}	-	-	0.179	0.202	0.206	0.181	0.132	0.073	0.024	0.003
20-29	1.26×10^{-2}	-	-	-	0.247	0.252	0.220	0.161	0.089	0.029	0.002
30-39	9.47×10^{-3}	-	-	-	-	0.334	0.292	0.214	0.118	0.038	0.004
40-49	6.31×10^{-3}	-	-	-	-	-	0.439	0.321	0.177	0.058	0.005
50-59	3.54×10^{-3}	-	-	-	-	-	-	0.571	0.315	0.102	0.012
60-69	1.52×10^{-3}	-	-	-	-	-	-	-	0.734	0.239	0.027
70-79	4.05×10^{-4}	-	-	-	-	-	-	-	-	0.896	0.104
80-89	4.19×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

[a]These lifetime risks apply to the entire population and represent one half the risk for females only.

Table 2B.2 Lifetime Lung Cancer Morbidity Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	5.70×10^{-3} 2.22×10^{-3}	-	0.125	0.143	0.168	0.188	0.176	0.125	0.059	0.014	0.002
10-19		1.95×10^{-3}	-	-	0.163	0.192	0.215	0.201	0.143	0.067	0.016	0.003
20-29		1.63×10^{-3}	-	-	-	0.229	0.257	0.240	0.171	0.080	0.020	0.003
30-39		1.26×10^{-3}	-	-	-	-	0.334	0.312	0.222	0.104	0.025	0.003
40-49		8.36×10^{-4}	-	-	-	-	-	0.468	0.333	0.157	0.038	0.004
50-59		4.43×10^{-4}	-	-	-	-	-	-	0.626	0.294	0.072	0.008
60-69		1.65×10^{-4}	-	-	-	-	-	-	-	0.788	0.192	0.002
70-79		3.52×10^{-5}	-	-	-	-	-	-	-	-	0.904	0.096
80-89		3.38×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a]Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.3 Lifetime Gastrointestinal Cancer Morbidity Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	2.48×10^{-2}	-	0.113	0.130	0.148	0.168	0.174	0.145	0.087	0.031	0.004
	Low	9.65×10^{-3}										
10-19		8.29×10^{-3}	-	-	0.146	0.167	0.190	0.196	0.163	0.098	0.034	0.006
20-29		7.08×10^{-3}	-	-	-	0.195	0.222	0.229	0.191	0.115	0.041	0.007
30-39		5.68×10^{-3}	-	-	-	-	0.277	0.286	0.237	0.144	0.050	0.006
40-49		4.12×10^{-3}	-	-	-	-	-	0.395	0.328	0.198	0.069	0.010
50-59		2.50×10^{-3}	-	-	-	-	-	-	0.543	0.328	0.115	0.014
60-69		1.14×10^{-3}	-	-	-	-	-	-	-	0.717	0.252	0.031
70-79		3.23×10^{-4}	-	-	-	-	-	-	-	-	0.891	0.109
80-89		3.50×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.4 Lifetime Thyroid Cancer Morbidity Risk (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	5.54×10^{-3}	0.105	0.198	0.180	0.160	0.135	0.105	0.070	0.035	0.011	0.001
10-19	4.26×10^{-3}	-	0.122	0.227	0.201	0.170	0.133	0.088	0.044	0.013	0.002
20-29	3.23×10^{-3}	-	-	0.145	0.264	0.224	0.174	0.115	0.058	0.018	0.002
30-39	2.32×10^{-3}	-	-	-	0.178	0.312	0.242	0.161	0.080	0.024	0.003
40-49	1.54×10^{-3}	-	-	-	-	0.225	0.368	0.244	0.122	0.037	0.004
50-59	8.98×10^{-4}	-	-	-	-	-	0.294	0.423	0.211	0.064	0.008
60-69	4.28×10^{-4}	-	-	-	-	-	-	0.393	0.453	0.138	0.016
70-79	1.46×10^{-4}	-	-	-	-	-	-	-	0.532	0.419	0.049
80-89	2.59×10^{-5}	-	-	-	-	-	-	-	-	0.722	0.278
90-99	1.54×10^{-6}	-	-	-	-	-	-	-	-	-	1.000

Table 2B.5 Lifetime Morbidity Risk for Skin Cancer (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	5.15×10^{-3}	-	0.244	0.215	0.182	0.145	0.105	0.065	0.030	0.009	0.005
	Low	2.01×10^{-3}										
10-19		1.58×10^{-3}	-	-	0.284	0.241	0.193	0.140	0.086	0.040	0.012	0.004
20-29		1.13×10^{-3}	-	-	-	0.337	0.269	0.195	0.120	0.057	0.017	0.005
30-39		7.47×10^{-4}	-	-	-	-	0.407	0.295	0.181	0.086	0.025	0.006
40-49		4.44×10^{-4}	-	-	-	-	-	0.498	0.306	0.145	0.043	0.008
50-59		2.22×10^{-4}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		8.61×10^{-5}	-	-	-	-	-	-	-	0.748	0.224	0.028
70-79		2.16×10^{-5}	-	-	-	-	-	-	-	-	0.894	0.106
80-89		2.28×10^{-6}	-	-	-	-	-	-	-	-	-	1.000

[a]Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.6 Lifetime Morbidity Risk for "Other" Cancers[a] (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	1.44×10^{-2}	-	0.132	0.149	0.166	0.176	0.165	0.122	0.066	0.021	0.003
	Low	5.60×10^{-3}										
10-19		4.82×10^{-3}	-	-	0.171	0.191	0.204	0.191	0.140	0.076	0.024	0.003
20-29		3.96×10^{-3}	-	-	-	0.231	0.246	0.230	0.169	0.091	0.029	0.004
30-39		3.07×10^{-3}	-	-	-	-	0.319	0.299	0.220	0.119	0.038	0.005
40-49		2.09×10^{-3}	-	-	-	-	-	0.439	0.324	0.174	0.056	0.007
50-59		1.17×10^{-3}	-	-	-	-	-	-	0.577	0.311	0.099	0.013
60-69		4.94×10^{-4}	-	-	-	-	-	-	-	0.737	0.235	0.028
70-79		1.30×10^{-4}	-	-	-	-	-	-	-	-	0.893	0.107
80-89		1.39×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus; but excluding skin and prostate cancer and all other cancers for which disease specific risk models have been developed.

[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.7 Lifetime Morbidity Risk from Benign Thyroid Nodules (Central Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	2.40×10^{-2}	-	0.222	0.201	0.177	0.149	0.116	0.078	0.040	0.012	0.005
10-19	1.80×10^{-2}	-	-	0.258	0.227	0.192	0.149	0.100	0.052	0.016	0.006
20-29	1.33×10^{-2}	-	-	-	0.307	0.259	0.201	0.135	0.070	0.022	0.006
30-39	9.26×10^{-3}	-	-	-	-	0.374	0.291	0.196	0.101	0.032	0.006
40-49	5.79×10^{-3}	-	-	-	-	-	0.465	0.313	0.162	0.051	0.009
50-59	3.09×10^{-3}	-	-	-	-	-	-	0.587	0.305	0.096	0.012
60-69	1.27×10^{-3}	-	-	-	-	-	-	-	0.739	0.233	0.028
70-79	3.33×10^{-4}	-	-	-	-	-	-	-	-	0.894	0.106
80-89	3.53×10^{-5}	-	-	-	-	-	-	-	-	-	1.000

Table 2B.8 Lifetime Breast Cancer[a] Morbidity Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	8.54×10^{-3}	-	0.164	0.194	0.201	0.170	0.129	0.084	0.043	0.013	0.002
	Low	1.22×10^{-3}										
10-19		1.04×10^{-3}	-	-	0.231	0.241	0.204	0.155	0.101	0.051	0.016	0.001
20-29		8.00×10^{-4}	-	-	-	0.313	0.265	0.201	0.132	0.066	0.020	0.003
30-39		5.49×10^{-4}	-	-	-	-	0.386	0.293	0.191	0.097	0.029	0.004
40-49		3.37×10^{-4}	-	-	-	-	-	0.477	0.312	0.157	0.048	0.006
50-59		1.76×10^{-4}	-	-	-	-	-	-	0.597	0.301	0.092	0.010
60-69		7.11×10^{-5}	-	-	-	-	-	-	-	0.746	0.228	0.026
70-79		1.80×10^{-5}	-	-	-	-	-	-	-	-	0.899	0.101
80-89		1.83×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] These lifetime risk estimates apply to the entire population and represent one half the risk for females only.
[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.9 Lifetime Lung Cancer Morbidity Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High	4.06×10^{-3}	-	0.163	0.190	0.203	0.181	0.131	0.081	0.038	0.011	0.002
	Low	5.80×10^{-4}										
10-19		5.19×10^{-4}	-	-	0.228	0.243	0.216	0.156	0.096	0.046	0.013	0.002
20-29		4.00×10^{-4}	-	-	-	0.315	0.279	0.203	0.125	0.059	0.018	0.001
30-39		2.74×10^{-4}	-	-	-	-	0.407	0.296	0.181	0.086	0.026	0.004
40-49		1.63×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		8.16×10^{-5}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		3.16×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0.026
70-79		7.94×10^{-6}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		8.43×10^{-7}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.10 Lifetime Gastrointestinal Morbidity Cancer Risk (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[a]	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	1.09×10^{-2} 1.56×10^{-3}	-	0.244	0.215	0.182	0.146	0.106	0.065	0.031	0.009	0.002
10-19		1.21×10^{-3}	-	-	0.284	0.241	0.193	0.140	0.086	0.041	0.012	0.003
20-29		8.67×10^{-4}	-	-	-	0.337	0.270	0.196	0.121	0.057	0.017	0.002
30-39		5.74×10^{-4}	-	-	-	-	0.407	0.296	0.181	0.086	0.026	0.004
40-49		3.40×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		1.70×10^{-4}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		6.61×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0.026
70-79		1.66×10^{-5}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		1.76×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		—	-	-	-	-	-	-	-	-	-	-

[a] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.11 Lifetime Morbidity Risk for "Other" Cancers[a] (Lower Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Dose Rate[b]	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
			0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	High Low	6.86×10^{-3} 9.80×10^{-4}	-	0.244	0.215	0.182	0.146	0.106	0.065	0.031	0.009	0.002
10-19		7.64×10^{-4}	-	-	0.284	0.241	0.193	0.140	0.086	0.041	0.012	0.003
20-29		5.47×10^{-4}	-	-	-	0.337	0.270	0.196	0.121	0.057	0.017	0.002
30-39		3.23×10^{-4}	-	-	-	-	0.407	0.296	0.181	0.086	0.026	0.004
40-49		2.14×10^{-4}	-	-	-	-	-	0.499	0.307	0.145	0.044	0.005
50-59		1.07×10^{-4}	-	-	-	-	-	-	0.612	0.290	0.087	0.011
60-69		4.17×10^{-5}	-	-	-	-	-	-	-	0.749	0.225	0.026
70-79		1.05×10^{-5}	-	-	-	-	-	-	-	-	0.895	0.105
80-89		1.10×10^{-6}	-	-	-	-	-	-	-	-	-	1.000
90-99		-	-	-	-	-	-	-	-	-	-	-

[a] Including lymphoma; multiple myeloma; cancer of the brain, kidney, bladder, ovary, and uterus; but excluding skin and prostate cancer and all other cancers for which disease specific risk models have been developed.

[b] Dose is assumed to be received at low dose rate in all time intervals except in the first interval.

Table 2B.12 **Lifetime Breast Cancer[a] Morbidity Risk (Upper Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.**

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy, R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	2.54×10^{-2}	-	0.085	0.110	0.154	0.185	0.182	0.152	0.095	0.033	0.004
10-19	2.32×10^{-2}	-	-	0.120	0.169	0.202	0.199	0.167	0.104	0.036	0.003
20-29	2.04×10^{-2}	-	-	-	0.192	0.229	0.226	0.189	0.118	0.040	0.006
30-39	1.65×10^{-2}	-	-	-	-	0.284	0.280	0.234	0.146	0.050	0.006
40-49	1.18×10^{-2}	-	-	-	-	-	0.391	0.327	0.204	0.070	0.008
50-59	7.19×10^{-3}	-	-	-	-	-	-	0.537	0.335	0.115	0.013
60-69	3.33×10^{-3}	-	-	-	-	-	-	-	0.723	0.248	0.029
70-79	9.21×10^{-4}	-	-	-	-	-	-	-	-	0.896	0.104
80-89	9.58×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

[a]These lifetime risk estimates apply to the entire population and represent one half the risk for females only.

Table 2B.13 Lifetime Lung Cancer Morbidity Risk (Upper Estimate) as a Function of Time Between Accident and Dose, and Fractions of Risk Expected to Occur Within Each of Ten Ten-Year Intervals.

Time Between Accident and Dose, t (yr)	Lifetime Risk for a Dose of 1 Gy R(1)	Time Since Accident, τ(yr)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
0-9	1.52×10^{-2}	-	0.125	0.143	0.168	0.188	0.176	0.125	0.059	0.014	0.002
10-19	1.33×10^{-2}	-	-	0.163	0.192	0.215	0.201	0.143	0.067	0.016	0.003
20-29	1.12×10^{-2}	-	-	-	0.229	0.257	0.240	0.171	0.080	0.020	0.003
30-39	8.61×10^{-3}	-	-	-	-	0.334	0.312	0.222	0.104	0.025	0.003
40-49	5.74×10^{-3}	-	-	-	-	-	0.468	0.333	0.157	0.038	0.004
50-59	3.05×10^{-3}	-	-	-	-	-	-	0.626	0.294	0.072	0.008
60-69	1.14×10^{-3}	-	-	-	-	-	-	-	0.788	0.192	0.002
70-79	2.42×10^{-4}	-	-	-	-	-	-	-	-	0.904	0.096
80-89	2.33×10^{-5}	-	-	-	-	-	-	-	-	-	1.000
90-99	-	-	-	-	-	-	-	-	-	-	-

Appendix A

BASE-LINE DEMOGRAPHIC AND MORTALITY DATA

Table A.1 1980 U.S. Population, All Races[a]

Age	Both Sexes	Male	Female
Total persons	226 545 805	110 053 161	116 492 644
Under 1 year	3 533 692	1 806 338	1 727 354
1 year	3 269 557	1 674 095	1 595 462
2 years	3 223 816	1 648 044	1 575 772
3 years	3 179 441	1 625 693	1 553 748
4 years	3 141 748	1 607 839	1 533 909
5 years	3 162 691	1 618 300	1 544 391
6 years	3 109 095	1 589 501	1 519 594
7 years	3 273 052	1 672 647	1 600 405
8 years	3 394 998	1 735 956	1 659 042
9 years	3 760 120	1 922 676	1 837 444
10 years	3 716 530	1 901 610	1 814 920
11 years	3 580 644	1 828 934	1 751 710
12 years	3 518 982	1 796 333	1 722 649
13 years	3 643 189	1 856 566	1 786 623
14 years	3 782 784	1 932 778	1 850 006
15 years	4 059 898	2 069 726	1 990 172
16 years	4 180 875	2 135 125	2 045 750
17 years	4 223 848	2 160 114	2 063 734
18 years	4 251 779	2 153 292	2 098 487
19 years	4 451 724	2 237 152	2 214 572
20 years	4 387 100	2 200 363	2 186 737
21 years	4 285 763	2 144 501	2 141 262
22 years	4 284 351	2 144 967	2 139 384
23 years	4 199 711	2 096 561	2 103 150
24 years	4 161 779	2 076 839	2 084 940
25 years	4 116 218	2 052 580	2 063 638
26 years	3 977 515	1 978 833	1 998 682
27 years	3 931 620	1 951 928	1 979 692
28 years	3 708 968	1 840 454	1 868 514
29 years	3 786 598	1 881 312	1 905 286
30 years	3 726 525	1 846 502	1 880 023
31 years	3 607 610	1 781 174	1 826 436
32 years	3 712 217	1 833 056	1 879 161
33 years	3 653 921	1 804 683	1 849 238
34 years	2 860 647	1 411 381	1 449 266
35 years	2 902 331	1 430 252	1 472 079
36 years	2 929 040	1 439 277	1 489 763
37 years	2 982 533	1 464 708	1 517 825
38 years	2 598 636	1 272 819	1 325 817
39 years	2 552 762	1 254 453	1 298 309
40 years	2 468 083	1 209 237	1 258 846
41 years	2 375 849	1 164 333	1 211 516
42 years	2 325 572	1 139 469	1 186 103
43 years	2 237 108	1 091 654	1 145 454
44 years	2 262 796	1 103 517	1 159 279
45 years	2 242 318	1 093 845	1 148 473
46 years	2 139 385	1 040 326	1 099 059
47 years	2 222 969	1 077 163	1 145 806
48 years	2 163 709	1 051 506	1 112 203
49 years	2 321 374	1 125 409	1 195 965
50 years	2 347 068	1 134 304	1 212 764
51 years	2 295 077	1 105 801	1 189 276
52 years	2 363 152	1 136 693	1 226 459
53 years	2 337 138	1 119 210	1 217 928
54 years	2 367 597	1 124 662	1 242 935
55 years	2 390 440	1 130 295	1 260 145
56 years	2 329 790	1 102 430	1 227 360
57 years	2 312 737	1 091 620	1 221 117
58 years	2 330 373	1 099 788	1 230 585
59 years	2 251 914	1 057 730	1 194 184
60 years	2 160 937	1 009 976	1 150 961
61 years	2 073 764	963 777	1 109 987
62 years	2 008 093	930 934	1 077 159
63 years	1 931 425	889 124	1 042 301
64 years	1 913 402	876 081	1 037 321
65 years	1 904 641	862 271	1 042 370
66 years	1 813 987	814 405	999 582
67 years	1 763 637	784 377	979 260
68 years	1 678 740	740 110	938 630
69 years	1 621 476	701 792	919 684
70 years	1 516 900	653 456	863 444
71 years	1 439 723	612 074	827 649
72 years	1 371 235	576 737	794 498
73 years	1 261 994	520 827	741 167
74 years	1 208 272	490 453	717 819
75 years	1 111 480	442 991	668 489
76 years	1 028 927	405 546	623 381
77 years	951 774	366 713	585 061
78 years	828 866	314 780	514 086
79 years	872 675	317 631	555 044
80 years	723 049	260 833	462 216
81 years	640 276	224 125	416 151
82 years	566 548	197 006	369 542
83 years	527 982	179 355	348 627
84 years	477 178	157 908	319 270
85 years	412 549	134 970	277 579
86 years	350 655	111 863	238 792
87 years	306 906	95 674	211 282
88 years	236 314	71 873	164 441
89 years	213 778	62 855	150 923
90 to 94 years	556 592	159 077	397 515
95 to 99 years	131 079	34 961	96 118
100 years and over	32 194	10 302	21 892
Median	30.0	28 8	31.2

[a]From General Population Characteristics, United States Summary, Census of Population, U.S. Department of Commerce, Bureau of the Census, 1980; Table 41.

Table A2 Number of Survivors, Out of 100,000 Born Alive, United States, 1978

AGE	TOTAL		
	BOTH SEXES	MALE	FEMALE
0	100,000	100,000	100,000
1	98,621	98,473	98,776
2	98,528	98,367	98,698
3	98,456	98,286	98,635
4	98,399	98,222	98,584
5	98,351	98,169	98,542
6	98,310	98,123	98,507
7	98,273	98,081	98,477
8	98,240	98,042	98,450
9	98,211	98,008	98,426
10	98,186	97,978	98,405
11	98,163	97,952	98,386
12	98,140	97,925	98,367
13	98,112	97,891	98,345
14	98,072	97,839	98,318
15	98,017	97,764	98,284
16	97,944	97,662	98,242
17	97,855	97,536	98,191
18	97,752	97,389	98,134
19	97,640	97,226	98,074
20	97,521	97,051	98,012
21	97,396	96,866	97,949
22	97,266	96,670	97,884
23	97,132	96,469	97,818
24	96,998	96,267	97,751
25	96,865	96,069	97,684
26	96,735	95,877	97,615
27	96,607	95,690	97,546
28	96,481	95,508	97,475
29	96,355	95,328	97,403
30	96,229	95,150	97,329
31	96,102	94,973	97,252
32	95,973	94,796	97,172
33	95,840	94,616	97,087
34	95,702	94,430	96,997
35	95,557	94,234	96,901
36	95,403	94,027	96,799
37	95,238	93,807	96,688
38	95,060	93,571	96,567
39	94,867	93,318	96,433
40	94,657	93,045	96,284
41	94,427	92,750	96,118
42	94,176	92,429	95,934
43	93,900	92,080	95,731
44	93,598	91,699	95,507
45	93,268	91,283	95,262
46	92,907	90,829	94,993
47	92,512	90,334	94,698
48	92,080	89,792	94,376
49	91,608	89,197	94,026

AGE	TOTAL		
	BOTH SEXES	MALE	FEMALE
50	91,091	88,543	93,647
51	90,526	87,824	93,235
52	89,910	87,037	92,788
53	89,243	86,184	92,306
54	88,527	85,268	91,788
55	87,761	84,289	91,234
56	86,945	83,249	90,643
57	86,075	82,141	90,010
58	85,135	80,947	89,326
59	84,108	79,643	88,579
60	82,981	78,213	87,759
61	81,744	76,648	86,858
62	80,401	74,953	85,876
63	78,966	73,144	84,824
64	77,462	71,246	83,720
65	75,902	69,277	82,572
66	74,292	67,244	81,381
67	72,621	65,141	80,134
68	70,873	62,954	78,814
69	69,024	60,664	77,396
70	67,056	58,259	75,862
71	64,971	55,742	74,208
72	62,772	53,126	72,431
73	60,469	50,413	70,507
74	57,992	47,608	68,410
75	55,397	44,720	66,121
76	52,671	41,764	63,638
77	49,828	38,760	60,971
78	46,890	35,733	58,138
79	43,882	32,710	55,163
80	40,832	29,721	52,070
81	37,766	26,797	48,881
82	34,712	23,973	45,615
83	31,696	21,284	42,291
84	28,747	18,767	38,923
85	25,891	16,462	35,524

[a]Life Tables, Vital Statistics of the United States, 1978 Volume II - Section 5; Table 5.2

Table A.3 Fraction of U.S. Population by Age, All Races

Age Interval	Total 1980[a] (226,545,805)	Female 1980[a] (116,492,644)	Age Interval	Total[b]	Female[b]
0-4	0.07215	0.0685	0-9	0.147	0.141
5-9	0.07371	0.0700			
10-14	0.08051	0.0800	10-19	0.181	0.174
15-19	0.09342	0.0894			
20-24	0.09409	0.0914	20-29	0.175	0.172
25-29	0.08616	0.0842			
30-34	0.07750	0.0763	30-39	0.133	0.132
35-39	0.06163	0.0610			
40-44	0.05150	0.0512	40-99	0.363	0.385
45-49	0.04894	0.0489			
50-54	0.05160	0.0522			
55-59	0.05126	0.0526			
60-64	0.04452	0.0465			
65-69	0.03875	0.0419			
70-74	0.02999	0.0338			
75-79	0.02114	0.0253			
80-84	0.01295	0.0164			
85-89	0.00670	0.0089			
90-94	0.00245	0.0034			
95-99	0.00057	0.0008			

[a] From General Population Characteristics, United States Summary, Census of Population, U.S. Department of Commerce, Bureau of the Census, 1980; Table 41

[b] From Chapter 4, Table 4.10; based on U.S. population, 1978

Table A.4. 1978 Cancer Mortality Rates (Deaths/Year per 100,000 Population)[a]

Age	All Cancer Excluding * Group[b]	Gastroin-Testinal	Lung Cancer	Breast Cancer	Other Cancer[c]
0-4	3.1	0.2	0	0	2.9
5-9	2.2	0.1	0	0	2.1
10-14	1.8	0.1	0	0	1.7
15-19	2.9	0.2	0	0	2.7
20-24	4.5	0.4	0.1	0.2	3.9
25-29	7.8	1.0	0.3	1.2	5.9
30-34	14.7	2.4	1.3	5.6	8.2
35-39	28.3	5.2	4.8	11.7	12.3
40-44	62.3	11.8	15.1	22.9	23.6
45-49	124.1	25.0	36.2	41.4	41.6
50-54	219.5	48.1	70.6	60.1	69.5
55-59	333.1	79.1	110.2	75.9	103.9
60-64	505.6	133.1	166.4	91.4	157.1
65-69	633.4	184.8	201.3	89.9	196.8
70-74	829.6	266.8	238.2	110.7	260.0
75-79	1041.1	376.3	245.0	128.4	340.8
80-84	1171.4	467.4	218.3	139.9	394.4
85-89	1178.5	513.3	147.1	157.2	408.6

[a]Source: Vital Statistics of the U.S., 1978

[b]* Group: Leukemia, Skin, Bone, Prostate, Thyroid

[c]Excluding * Group and Gastrointestinal, Lung, and Breast

Table A.5. 1973-1977 Cancer Incidence Rates (New Cases/Year per 100,000 Population)[a]

Age	All Cancer Excluding * Group[b]	Gastroin-testinal Cancer	Lung Cancer	Breast Cancer (Females)	Other Cancer[c]
0-4	10.2	0.7	0	0	9.5
5-9	5.8	0.2	0	0	5.6
10-14	6.5	0.3	0.1	0	6.1
15-19	11.5	0.5	0.2	0.2	10.7
20-24	20.4	1.3	0.2	1.1	18.3
25-29	33.2	2.4	0.7	8.3	25.9
30-34	55.4	5.5	2.3	26.7	34.1
35-39	93.5	11.9	7.1	57.2	45.3
40-44	170.4	24.9	20.4	106.2	70.6
45-49	300.6	50.2	47.7	173.8	113.7
50-54	457.3	89.4	79.8	195.9	187.2
55-59	682.1	155.5	130.2	228.9	277.6
60-64	910.5	240.5	185.6	251.2	351.8
65-69	1163.4	351.2	235.5	282.9	420.1
70-74	1399.4	475.2	258.5	302.0	489.6
75-79	1646.9	617.9	255.9	338.0	564.4
80-84	1733.3	708.9	211.4	350.0	586.2
85-89	1831.0	795.6	166.0	376.3	611.3

[a]Source: Cancer Incidence and Mortality in the United States, 1973-77 (SEER)

[b]* Group: Leukemia, Skin, Bone, Prostate, Thyroid

[c]Excluding * Group and Gastrointestinal, Lung, and Breast

Table A.6 1978 U.S. Age-Specific Population and Births

Age (yr)	White Males		White Females		Births[c]
	Population[a]	$_nL_x$[b]	Population[a]	$_nL_x$[b]	
<1	7182	98825	6833	99072	0
1- 5	27145	394014	25814	395283	0
5- 9	37868	491440	36124	493314	0
10-14	41955	490604	40116	492749	29
15-19	47690	488360	46211	491793	2418
20-24	46116	484072	45597	490325	5819
25-29	41170	479688	41033	488818	5472
30-34	36612	475820	36723	487151	2552
35-39	29769	471426	30643	484938	648
40-44	25740	465182	26583	481430	111
45-49	25931	455217	26912	475598	6
50-54	27007	439187	28783	466511	0
55-59	25624	414767	27908	452973	0
60-64	21282	378308	24028	432730	0
65-69	18012	328269	22539	404187	0
70-74	12944	265672	17890	364287	0
75-79	7882	192039	12488	305546	0
80-84	4675	117620	8661	226259	0
≥85	3233	89129	7278	246257	0

[a]Number of white males or white females out of 1,000,000.

[b]Number of years of life in this age group experienced per year by a hypothetical population of 100,000 livebirths under the 1978 Life Table for the U.S.

[c]Births per year from mothers in specified age group in a total population of 1,000,000. Births have been increased by a factor of 1.25 from the 1978 U.S. figures to establish a stable population.

Table A.7 Live Births By Age of Mother, All races, United States, 1980

Age of Mother	Live Births[a] U.S. 1980
All Ages	3,612,258
< 15	10,169
15-19	552,161
20-24	1,226,200
25-29	1,108,291
30-34	550,354
35-39	140,793
40-44	23,090
45-49	1,200

[a]Source: Monthly Vital Statistics Report, Advance Report of Final Natality Statistics, 1980, Vol. 31, No.8, Supplement, November 30, 1982.

Part II: Scientific Basis for Health Effects Models

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Chapter 1. Early Occurring and Continuing Effects

Chapter 1

EARLY OCCURRING AND CONTINUING EFFECTS

B.R. Scott and F.F. Hahn

Executive Summary

This chapter deals with health-risk estimates for early and continuing effects of exposure to ionizing radiations that could be associated with light water nuclear power plant accidents. Early and continuing effects considered are nonneoplastic diseases and symptoms that normally occur soon after radiation exposure, but may also occur after years have passed. They are generally associated with relatively high (greater than 1 Gy) doses. For most of the effects considered, there is a practical dose threshold. A possible exception may be morbidity effects of exposure *in utero*.

Early effects may result from external total-body irradiation, partial-body irradiation, or specific-organ irradiation as may occur after inhalation or ingestion of radionuclides. All possible types of exposure are considered. Health risks are considered for effects associated with irradiation of single organs, although the radiation exposure may involve more than one organ. Using the organ-specific approach facilitates combining the effects of external and internal irradiation.

Organs of primary interest, because of their high sensitivity or the likelihood of receiving a large radiation dose, are bone marrow, gastrointestinal tract (i.e., small intestines and colon), thyroid glands, lungs, skin, gonads, eyes. *In utero* exposure of the fetus is also considered.

New data and modeling techniques available since publication of the Reactor Safety Study (WASH 1400, 1975) were used along with data cited in the Reactor Safety Study to develop improved health-risk models for morbidity and mortality. The improved models are applicable to a broader range of accident scenarios than those developed in the Reactor Safety Study, provide a more detailed treatment of dose protraction effects, and include morbidity effects not modeled in the Reactor Safety Study.

Morbidity effects that were modeled in both the Reactor Safety Study and this chapter are (1) prodromal vomiting, (2) permanent sterility in females, (3) temporary sterility in males, and (4) growth retardation (small head size) after irradiation *in utero*. Additional morbidity effects modeled in this chapter include: (1) diarrhea, (2) radiation thyroiditis, (3) hypothyroidism, (4) skin erythema, (5) transepithelial injury of the skin, (6) mental retardation after irradiation *in utero,* and (7) cataracts. Available information was not sufficient to model permanent sterility in males nor temporary sterility in females.

As in the Reactor Safety Study, only beta and gamma radiations are considered and three modes of death are modeled: (1) death associated with injury to the bone marrow, (2) death associated with injury to the intestines (representative of the gastrointestinal tract), and (3) death associated with injury to the lungs.

Also as in the Reactor Safety Study, we consider the reduction in lethality risks due to medical intervention. The same three categories of medical treatment are considered as were used in the Reactor Safety Study: minimal, supportive, and intensive (called "heroic" in the Reactor Safety Study). Minimal treatment involves basic first aid. Supportive treatment includes antibiotic therapy, blood transfusions, and reverse isolation. Intensive treatment includes bone marrow transplantation, in addition to supportive treatment.

More improvements in the treatment of irradiated individuals have been developed since the publication of the Reactor Safety Study. Therefore, the categories of medical treatment discussed in this chapter should not be regarded as dictates for physicians to follow but rather

are intended to be used as guides in estimating the number of deaths to be expected following a light water nuclear power plant accident.

While lethality models are provided for the three categories of medical treatment (minimal, supportive, and intensive), the uncertainty in the model predictions increases as the intensity of the treatment increases.

A number of different types of risk estimators (mathematical functions used to generate risk estimates) were used in the Reactor Safety Study to arrive at the overall model for morbidity and mortality effects. These risk estimators included: (1) the bimodal-Gaussian type used for lethality associated with injury to the bone marrow as well as for prodromal vomiting; when plotted on probability paper, this type of model looks somewhat like a hockey stick; (2) the unimodal-Gaussian type, which appears as a straight line when plotted on probability paper, was used for temporary sterility in males; (3) the linear-threshold type was used for both morbidity and mortality effects of irradiation of the gastrointestinal tract; (4) the power function type, which looks like a straight line when plotted on logarithmic paper, was used for prenatal and neonatal mortality as well as for morbidity effects of irradiation of the lungs; (5) other complex types whose mathematical forms were not stated were used for permanent sterility in females and for growth retardation after *in utero* exposure. All of these different types of risk estimators used in the Reactor Safety Study have been replaced by a single Weibull-type estimator. Use of a single type of risk estimator provides for a systematic representation of all mortality and morbidity risks.

The Weibull-type function used to estimate risk basically depends on two parameters, in addition to dose: (1) the shape parameter V, which determines the shape of the dose-effect relationship, and (2) the dose D_{50}, which is the dose expected to effect 50% of those exposed. For lethal effects, it represents the lethal dose to 50% of the population (LD_{50}), while for morbidity effects, it represents the effective dose to 50% of the population (ED_{50}). Use of the notation D_{50} allows for a systematic characterization of both mortality and morbidity effects.

Rather than working with the organ-specific absorbed dose D in Gy, it is sometimes more convenient to work with dimensionless dose units arrived at by dividing the dose D by the median dose D_{50}. The general expression for risk in terms of the dimensionless doses D/D_{50} and shape parameter V is given by

$$\text{Risk} = 1 - \exp\left[-ln(2)(D/D_{50})^{V}\right].$$

A slightly more complicated relationship is used to account for dose protraction effects.

For the dimensionless dose units used, a value of 1 represents a median lethal dose, while a value of 0.5 represents one-half the median lethal dose. However, because of the threshold-type risk functions for most early and continuing effects of irradiation, one-half a median lethal dose is generally associated with a risk considerably smaller than one would predict by dividing the risk of 0.5 by 2 to get 0.25. For lethality from injury to the bone marrow, one-half of a median lethal dose leads to a central risk estimate of approximately 0.0007 based on the threshold-type model used in the chapter. Exposure of 100 individuals to such a dose would lead to no expected deaths.

A generic method is used to model dose-protraction effects. Two general categories of exposure are considered: (1) brief exposure mainly to external cloud-shine (i.e., from a passing

radioactive cloud) and ground-shine (i.e., from the radionuclide-contaminated ground surface) gamma rays followed by (2) protracted internal exposure to mainly low-LET (linear energy transfer) radiations emitted by inhaled and ingested radionuclides. Beta and gamma radiations are treated as having equal effectiveness.

It is assumed that following the brief exposure period, the dose rates to critical organs decrease as follow-up time increases. In some cases, the overall period of dose protraction is separated into more than one component period to provide for a more precise treatment of dose protraction effects. The total number of periods considered depends on the availability of data and information related to dose protraction effects.

For lethality considerations, injury to the bone marrow is the most important because lethal doses are relatively small in comparison to lethal doses to other organs. For example, approximately three times more dose to the lungs is required for lethality as is required for the bone marrow, and approximately four times more dose to the intestines. Even higher doses would be required to the central nervous system. Because lethal doses to the central nervous system would also be accompanied by lethal doses to the bone marrow, we do not include a risk function specifically for lethality from injury to the central nervous system. Similarly, large areas of the skin would have to be irradiated by beta-radiation to pose a lethality risk, and it is unlikely that such large areas of the skin would be irradiated following a nuclear power plant accident. Most individuals would be protected to a large extent by their clothing. For this reason, lethal injury from beta skin burns is not expected to be a significant problem.

The bone-marrow-injury mode of lethality can be used to illustrate how dose protraction effects are modeled. The same approach is used for the other lethality modes (injury to the intestines, injury to the lungs) as well as for the morbidity effects considered. For the bone-marrow-injury mode of lethality, we consider a brief (0- to 1-day) relatively high dose rate exposure period followed by two consecutive periods of dose protraction: (1) protracted exposure at lower dose rates between 1-14 days, and (2) protracted exposure at even lower dose rates between 14-30 days. Because this approach is based on the assumption that dose rates decrease progressively for the three consecutive exposure periods, a different median lethal dose (D_{50}) is assigned for the three periods. The D_{50} values are based on data for exposure of humans and on dose protraction factors derived from studies with laboratory animals. The shape parameter is assumed not to depend on dose rate and a single value is used. We were not able to reject the hypothesis of a single value for V using presently available data. Also with a single value for V for a given effect, the mathematical structure of the functions used to estimate risks is less complicated.

The generic hazard-function method used to model the impact of dose protraction is based on what is called the cumulative hazard H. The cumulative hazard H is related to the risk (Risk) by the equation

$$\text{Risk} = 1 - exp(-H).$$

Different types of mathematical functions can be used to represent H. Because of its versatility, we have used the Weibull-type function for the cumulative hazard and therefore we are also using a Weibull-type risk function. For brief exposure, H has the form

$$H = ln(2)(D1/D_{50})^V$$

where $D1$ is the dose delivered in the brief exposure period considered. With the hazard-function modeling approach used, one first arrives at an estimate of the cumulative hazard H; then the above equation for risk can be used to arrive at risk indirectly.

Based on the hazard-function modeling approach used, and the assumption that the shape parameter V does not depend on dose rate, the cumulative hazard HB for lethality associated with injury to the bone marrow can be given in terms of the brief 0-1-day dose $D1$ to the bone marrow, the protracted 1-14-day dose $D2$, and the protracted 14-30-day dose $D3$ by:

$$HB = ln(2)[D1/3.4 + D2/7 + D3/14]^{10}$$

where the doses are in Gy and the 3.4 (Gy), 7 (Gy), and 14 (Gy) are best estimates of the median lethal doses for lethality associated with injury to the bone marrow of humans following brief exposure over about 1 day, for protracted exposure over about 14 days, and for protracted exposure over about 30 days, respectively. The 30-day cutoff on dose to the bone marrow is based on studies with laboratory animals that have shown that the critical period of internal dose accumulation is about 30 days. Note that the ratios D1/3.4, D2/7, and D3/14 are also dimensionless D_{50} doses. Thus, the procedure for protracted exposure differs from that for brief exposure only in that the dimensionless dose D1/3.4 for brief exposure is replaced by the sum of three such doses for the three periods of dose accumulation considered. One adds the dimensionless doses to arrive at a total dimensionless dose in D_{50} units.

The protracted 1-14-day dose, which is mainly due to inhaled and ingested radionuclides, is treated as being 3.4 Gy/7 Gy or about one-half as effective as the brief 0-1-day dose, which is mainly due to external cloud- and ground-shine gamma rays. Similarly, the protracted 14-30-day dose is treated as being 3.4 Gy/14 Gy or about one-fourth as effective as the brief 0-1-day dose. In this respect, the hazard-function modeling approach in its present application (i.e., with constant shape parameter V) is quite similar to what was done in the Reactor Safety Study but may be regarded by some as more formal. A similar approach can be used when the shape parameter V depends on dose rate, LET, or on both, but with more complicated results.

The same approach was used to arrive at cumulative hazards for lethal injury to the intestines (small and large intestines treated separately) and lung as well as for all morbidity effects.

An advantage in this method of modeling is the treatment of dose protraction effects. Another advantage is in modeling threshold type relationships for the combined effects of both high and low LET radiations when the relative biological effectiveness of the high LET radiation depends on dose; however, this latter advantage does not apply to this chapter because the high LET dose is not expected to be significant.

To calculate total lethality risk from all early and continuing effects, the cumulative hazards for each possible lethal mode of injury (bone marrow, intestines, and lung) are added to arrive at an overall lethality hazard called H_{early}. The central estimate of risk of lethality from all early and continuing effects is then given by

$$\text{Risk} = 1 - exp(-H_{early}).$$

When reliable data based on exposure of humans were available, they were used to estimate the shape parameter V and/or D_{50} for morbidity and mortality effects. When such data were not available or were ambiguous, data from exposure of laboratory animals were used to estimate these parameters. However, only reasonable cross-species extrapolations were made. For example, in constructing the risk estimator for lethality associated with injury to the bone marrow, laboratory animal data were used to estimate the shape parameter V and a value of approximately 10 was obtained. The D_{50} estimate of 3.4 Gy is the same as was used in the Reactor Safety Study and is based solely on exposure of humans. Laboratory animal data were also used to assess the impact of dose protraction, and age at exposure (for lung irradiation only) on the parameter D_{50}. As was the case for dose rate effects, it was assumed that the parameter V does not depend on these covariates. Presently, available data are not sufficient for rejection of this assumption and its use leads to simplification of the health effects model.

Several sources of uncertainty that could have an effect on accuracy of the risk estimates include: (1) uncertainty in dose, (2) statistical errors associated with model parameters, (3) possible systematic errors associated with use of Weibull-type functions, (4) uncertainty about dose protraction effects, (5) uncertainty associated with cross-species extrapolation, (6) uncertainty about the effect of medical intervention, and (7) uncertainty about the makeup of the population at risk (e.g., the presence of sensitive subgroups).

An investigation of the effect of uncertainty in dose is beyond the intended scope of this chapter. To do so would require development of computer software to predict population and organ dose distribution following a nuclear power plant accident and additional software to predict the subsequent health impacts. Others are currently preparing such software and, when completed, it can be used to conduct sensitivity analyses to investigate the impact of uncertainties in dose.

The uncertainties in dose-response are accounted for by modifying the values of the parameters in the hazard functions. To generate an approximate upper bound for risk from bone marrow syndrome, the D_{50} is shifted downward from 3.4 to 2.8 Gy and the shape parameter is shifted from 10 to 15. To generate an approximate lower bound for risk from bone marrow syndrome, the D_{50} is shifted upward from 3.4 to 4.0 Gy and the shape parameter is shifted from 10 to 6.6. The considerations leading to these choices are described in detail within the chapter.

We concentrated on developing uncertainty estimates for bone marrow syndrome because it is likely to be responsible for most early deaths. Upper and lower bounds were not developed for other effects. If the initial runs of the new computer codes identify causes of death or illness that are as important as bone marrow syndrome, then future efforts should be directed toward development of appropriate uncertainty estimates for these effects.

The risk estimators discussed in the chapter were developed solely for nuclear power plant accident consequence modeling. Taken together, the models permit analysis of the early health effects of nuclear power plant accidents. However, individual risk estimators, if used out of the context of nuclear power plant accident consequence modeling, may function in a less-than-satisfactory manner. We suggest that they be applied only in the realm of nuclear power plant accident consequence modeling or for closely related problems.

1.1 Introduction

1.1.1 Benefits of Revision

This chapter summarizes health-risk estimates for early and continuing effects of exposure to ionizing radiations associated with light water nuclear power plant accidents that have been developed to improve upon those used in the Reactor Safety Study (WASH 1400, 1975). The estimates used in the Reactor Safety Study were based on data and modeling techniques available before 1975. Since publication of that study, new data and modeling techniques have become available and were considered in developing the health-risk estimates that follow.

The new health-risk models are applicable to a broader range of accident scenarios than those developed in the Reactor Safety Study. They can also be used to estimate the probability of effects over a wider range of dose rates, and they include morbidity effects not included in the original Reactor Safety Study health effects model. Further, the method used to develop the new health-risk estimates is generic and, with additional parameters, can be used to evaluate other types of nuclear power plant accidents, including those involving plutonium and thorium fuel cycles. During ensuing years as more research results become available, parameters used in the health-risk estimates may be replaced by improved ones without having to change the basic mathematical structure of the risk estimators.

1.1.2 Approach

1.1.2.1 Sources of Information

Information from the Reactor Safety study is used extensively as a basis for developing the health-risk estimates. Throughout this chapter, data based on radiation exposures of people are used when applicable human data are available and the uncertainty in the data is small. However, for specific types of exposures where data from studies in humans are too uncertain or where no data are available, information based on exposure of laboratory animals has been used in combination with available data for exposure of humans. For example, in predicting mortality risk from total-body exposure to external radiation, data from animal studies are used to determine the shape of the dose-effect curves, whereas the best estimate of the median lethal dose that can be obtained from studies of exposed humans is used to establish the position of the dose-effect curve. When available, data for determining the likely impact of dose protraction were used, but when such data were not available, published dose-rate-dependent effects models were used to estimate dose rate protraction factors.

In most cases, information on morbidity was too limited to support reliable estimates of dose rate effects. Also, sensitive subpopulations (for example, children, the sick, etc.) are expected to make up a small but significant part of the exposed population at risk, for both mortality and morbidity. However, there is not sufficient information available to derive reliable risk estimates for specific subpopulations, except perhaps for effects of irradiation of the lungs of adolescents compared to adults. Uncertainties in risks from radiation exposure were incorporated by using upper and lower bounds for risks. Little quantitative information is available on the likely effects of medical treatment for exposed individuals, but where possible the effect of medical treatment on survival was considered.

1.1.2.2 Characteristics of Types of Exposures and Effects

Early and continuing effects considered in this chapter are nonneoplastic diseases and symptoms that normally occur soon after radiation exposure, but may even occur after years have passed. They are generally associated with relatively high radiation doses; and the severity is less with smaller radiation dose. This implies that there is usually a practical dose threshold for early effects below which no effects should be seen.

Early effects may result from external total-body irradiation, partial body irradiation, or specific organ irradiation such as that resulting from ingestion or inhalation of radionuclides. They may also result from a combination of these exposures. All possible types of exposure are considered in the model. Health risks are considered for effects that occur in single organs, although the radiation exposure may involve several organs or the total body. Using a specific-organ approach facilitates combining the risks from external irradiation and from internal emitters. The data available for predicting some organ effects, such as that resulting from high-level, brief exposures to bone marrow, are based on total-body exposure of humans. Thus, possible interactions of effects among organs may already be accounted for in this exposure mode. No information exists to determine possible interactions among organs where exposure is from both external irradiation and internal emitters.

High external radiation doses to the total body cause inflammatory and degenerative lesions in the most sensitive organs. Irradiation from internally deposited radionuclides causes lesions in the organs where the dose is delivered. Organs of primary interest, because of their high sensitivity or the likelihood of receiving a large radiation dose are bone marrow, gastrointestinal tract, thyroid gland, lungs, skin, gonads, and eyes. The fetus if also of primary interest.

1.1.2.3 Hazard Function Approach

A hazard function approach was used to derive risk estimates for effects in various organs of the body and to determine total risk resulting from exposures to several organs. A detailed description of the approach for combining risks due to exposure of several organs is provided in Section 1.3. The cumulative hazard (H) is related to risk of mortality or morbidity in an irradiated population. If the cumulative hazard is known, the risk can be calculated. Cumulative hazards can be defined by a number of different mathematical functions. A two-parameter Weibull function is used here to describe the dose-effect relationship because it adequately represents the available data and facilitates computer programming for predicting early effects.

The general expression used for cumulative hazard is:

$$H = ln(2)\,(D/D_{50})^V \tag{1.1}$$

where D = radiation dose over specified time, D_{50} = dose for producing an effect of interest in 50% of individuals, and V = shape parameter that determines the steepness of the slope of the dose-effect curve. This expression is used to derive risk estimates of the different organs affected, as given by the expression:

$$\text{Risk} = 1 - e^{-H} \tag{1.2}$$

The dose-effect relationship described by this equation is plotted in several ways for a constant value of V in Figure 1.1. On probability graph paper, the dose-effect curves will appear as parallel straight lines with a slope given by the value of V; the D_{50} determines where each curve is located. When plotted on rectilinear graph paper, the dose-effect curves will take on a sigmoidal shape and may not appear parallel. If risks are plotted on a rectilinear scale vs. dose on a logarithmic scale for a constant value of the shape parameter V but for different values of the D_{50}, the resultant curves will appear parallel. One can go from one of these parallel curves to another merely by scaling according to the ratio of the D_{50} values. For mortality the dose-effect curves are quite steep.

Risk estimates of the type represented by equation (1.2) behave as though there is a threshold dose if the dose-effect curve is steep, that is, V is > 3. Therefore, risk estimates of this form are useful for the evaluation of risks associated with early and continuing effects of radiation exposure, as they lead to a threshold-type relationship even though data are insufficient for determining the actual threshold. Determination of the value of a threshold dose for mortality from early effects with a reasonable degree of accuracy would require data from the exposure of large numbers of individuals to relatively large radiation doses and the doses would have to be known accurately. No such data exist.

The problem of estimating a threshold dose accurately is similar to that in low-dose extrapolation of carcinogenic risk. However, unlike low-dose carcinogenic risk assessment, where one is concerned about many individuals each receiving a small dose, the concern with early effects is typically with the exposure of a smaller number of individuals to relatively large doses. Except for effects of *in utero* irradiation, individuals receiving relatively small doses (tenths of Gy) would incur no significant risk of early and continuing effects of irradiation.

Throughout this chapter, the median dose for each effect (D_{50}) and the shape parameter (V) are given. A different set of parameters is needed for predicting effects of radiation doses delivered over different time periods to account for dose protraction effects. Medical treatment may also alter the response and therefore requires additional parameters. In the future, more parameters may be obtained as more data become available on factors that influence the dose-response relationship.

A simple example of the use of the cumulative hazard function and calculations of risk is as follows. Assume that a dose equal to the median lethal dose is received by a population ($D/D_{50} = 1$) and that $V = 10$. The cumulative hazard and the risk can be calculated as follows:

$$H = ln(2)\,(D/D_{50})^V$$

$$H = 0.693\,(1)^{10} = 0.693$$

$$\text{Risk} = 1 - e^{-H} = 1 - e^{-0.693} = 1 - 0.5 = 0.5$$

The risk from being exposed to a median lethal dose (D_{50}) is 0.5, as would be expected.

The advantage of using the hazard function approach is apparent when the risks from a complex exposure situation must be determined (for example, brief total-body irradiation followed by protracted irradiation by internally deposited radionuclides). With the hazard

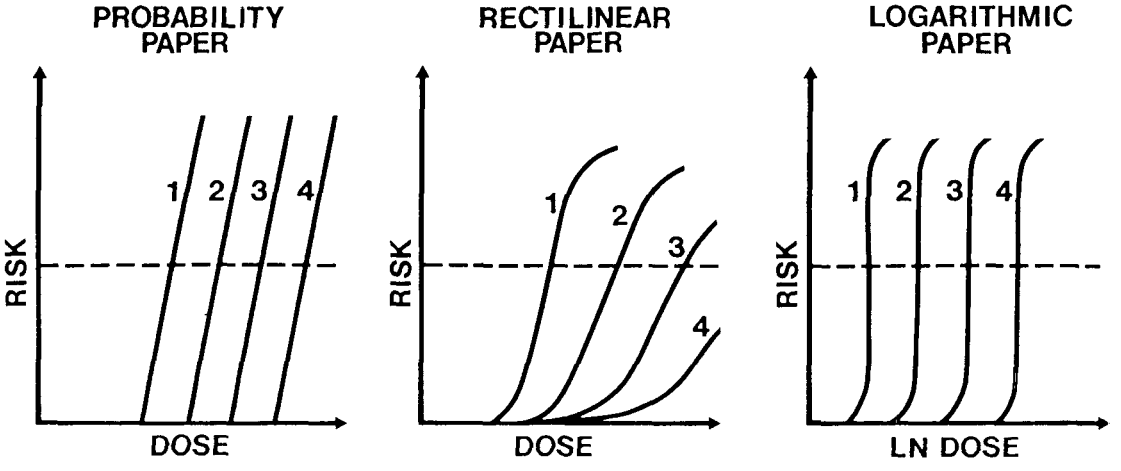

Figure 1.1 Dose-effect relationships based on a two parameter Weibull hazard function model. Risk is given by risk = 1-exp($-\ln(2)\ (D/D_{50})^{v}$). A family of curves is shown for a constant value of the shape or slope parameter v, and for various values of the D_{50}. Note that the curves are parallel plotted on probability paper and on logarithmic paper.

function approach, the increments in cumulative hazard for each component of the exposure are summed rather than estimating the total risk by first adding dose equivalents. For cases where the relative biological effectiveness (RBE) or dose rate protraction factors are not constant, the hazard function modeling approach can be used whereas the dose equivalent system cannot.

The cumulative hazard calculated after brief exposure (D_b) followed by a protracted exposure (D_p) would be expressed:

$$H = ln(2)\,(D_b/D_{b_{50}} + D_p/D_{p_{50}})^V \tag{1.3}$$

where $D_{b_{50}}$ = median dose for effect for brief exposure, and $D_{p_{50}}$ = median dose for effect for protracted exposure. The above relationship is valid if the dose-effect curves have the same slope; otherwise a slightly more complicated relationship arises (Scott, 1983, 1984). Two sample calculations are presented below to illustrate how the effects of brief and protracted doses are combined.

Sample Calculation:

$$D_b/D_{b_{50}} = 0.1$$

$$D_p/D_{p_{50}} = 0.1$$

$$V = 10$$

$$H = 0.693\,(0.1 + 0.1)^{10} = 7.1 \times 10^{-8}$$

$$\text{Risk} = 1 - \exp\,(-7.1 \times 10^{-8}) = 7 \times 10^{-8}$$

This sample calculation illustrates how the Weibull risk functions used in this chapter provide an effective threshold. If 1000 people were exposed to this scenario, there would be no expected early deaths.

Sample Calculation:

$$D_b/D_{b_{50}} = 0.5$$

$$D_p/D_{p_{50}} = 0.5$$

$$V = 10$$

$$H = 0.693\ (0.5 + 0.5)^{10} = 0.693$$

$$\text{Risk} = 1 - e^{-H} = 1 - e^{-0.693} = 1 - 0.5 = 0.5$$

This result implies that half a D_{50} for brief exposure followed by half a D_{50} for protracted exposure results in a risk of 0.5. Information from animals is not available to verify this result. The procedure appears to be appropriate, however, based on the known radiobiologic principles of nonlinearity of the dose-effect function and the existence of a practical threshold. This approach does predict accurately the cell killing by combined exposure to neutrons plus x-rays or alpha-radiation plus x-rays (Scott 1983, 1984).

A third example calculation is given to illustrate an important point about use of the assumption of independent effects of brief and protracted doses.

Sample Calculation:

$$D_b/D_{b_{50}} = 1$$

$$D_p/D_{p_{50}} = 1$$

$$V = 10$$

$$H = 0.693\ (1 + 1)^{10} = 710$$

$$\text{Risk} = 1 - e^{-H} = 1 - e^{-710} = 1$$

This result indicates that a D_{50} for brief exposure followed by a D_{50} for protracted exposure yields a risk of 1. If it were assumed that the two doses (D_b and D_p) acted independently, the calculated surviving fraction would be $0.5 \times 0.5 = 0.25$, so the calculated risk would be $1 - 0.25 = 0.75$, compared to the risk of 1 calculated by the hazard function technique. This illustrates how use of the hazard function modeling approach estimates the total risk of dependent effects from different types of radiation dose patterns.

A fourth example illustrates how the total risk of death from effects in different organs of the body can be determined by use of a second hazard function technique. The cumulative hazards for each cause of death are added to determine the total mortality risk. A sample calculation for risk of death from injury to the hematopoietic system (HB), gastrointestinal tract (HGI), and lungs (HL), where HB, HGI, and HL are respective cumulative hazards for lethality, is as follows:

Sample calculation:

$$HB = 0.5$$

$$HGI = 0.5$$

$$HL = 0.5$$

$$\text{Total Hazard} = 0.5 + 0.5 + 0.5 = 1.5$$

$$\text{Total Mortality Risk} = 1 - e^{-1.5} = 1 - 0.223 = 0.777$$

The function HB may account for some interorgan effects because it is derived from data for total-body exposure. With these hazard function techniques, many different causes of death and modifying factors can be used in the calculation if there is good supporting information.

Cumulative hazards for different morbidity effects (that is, sterility, hypothyroidism, cataracts) should not be added.

1.1.2.4 Effect of Model Selection

Because of the steepness of the dose-effect relationships for most early effects, the choice of model for organ-specific effects is not as critical as one might expect. Almost any plausible sigmoidal type function would lead to about the same number of expected deaths, except in the tail region of the dose-effect curve, where none of the model predictions can be validated. Other models could have been used (Jones, 1981; Goldman and Raabe, 1977; Wells, 1976; Filipy *et al.*, 1980) including the tolerance-dose-distribution models (logit, gamma, extreme value, normal, etc.). All of these models lead to sigmoidal curves, except the model of Jones and the graphical model of Wells in which the dose-effect curve is replaced by regions of uncertainty and certainty for lethality and survival.

The major advantage of the hazard function model over these other models is in predicting the effects of dose protraction. In addition, the hazard function approach simplifies computer programming necessary in the development of the integrated health effects models.

1.2 Risk Estimates for Early and Continuing Effects in Specific Organs

The objective in the following sections is to discuss briefly the effects seen after low linear energy transfer (LET) irradiation of various organs and then to establish both the median dose of external photons or internal beta radiation needed to cause each effect and the shape of each dose-effect relationship. The information from the Reactor Safety Study was used in conjunction with pertinent new data to establish the D_{50} and the shape of the response curve. The risk of effects on individual organs can be combined to develop total risk from external and/or internal irradiation.

Risk estimates are considered for specific organs, although the radiation exposure may involve several organs or the total body. This approach facilitates combining the risks from external and internal irradiation. The procedure for combining the risks from several organs is described in Section 1.3.

The dose-effect relationships are considered by individual organ because they can usually be related to radiation damage in a specific critical organ. Interaction effects among organs may occur in response to radiation injury. For example, induction of the classic gastrointestinal syndrome involves irradiation of both the gastrointestinal tract and the bone marrow. The specific risks for such interactions cannot be determined, but are accounted for where dose-response relationships are based on total-body exposures in humans.

Risk estimates for deaths and illnesses for each organ are determined where sufficient data are available. In addition, separate risk estimates are provided for doses delivered briefly (in one day) and for doses received during subsequent periods of protracted exposure. The time periods vary for different organs, depending on the period over which a dose might be delivered. The brief exposures primarily involve total-body irradiations, and the protracted exposures primarily involve doses from internally deposited radionuclides.

1.2.1 Effects of Total-Body Irradiation

The effects of total-body irradiation in humans have been well characterized and reviewed in detail (Cronkite and Bond, 1958; Bond *et al.*, 1965; Langham, 1967; UNSCEAR, 1982). In this report, the dose-effect relationships will be considered organ-by-organ; however, much of the information that forms the basis for risk estimates for bone marrow and

gastrointestinal tract is derived from studies of people receiving total-body exposure.

Most of the symptoms induced by total-body irradiation are from injuries in specific organs. After very high doses (> 20 Gy), in a short period of time, the predominant signs are those of hypotensive shock followed by anoxic convulsion, coma, and early death. Death will typically occur in less than 8 hours without antishock therapy and within 30 to 48 hours when antishock therapy is given. These effects are related to injury of the nervous and cardiovascular systems. At lower doses (6-20 Gy), the predominant symptoms are those of overwhelming sepsis and toxemia. Nausea, vomiting, diarrhea, dehydration and death may also occur. At even lower doses (2-6 Gy), signs of infection and anemia may occur and are both related to bone marrow depression with resulting decrease of blood cell formation. There is considerable overlap in the symptoms and mechanisms of death in these three dose ranges. However, the median lethal dose for total-body irradiation is in the dose range that causes death related to bone marrow depression. Death is due to infection and toxemia secondary to agranulocytosis and immune depression.

A group of symptoms of acute gastrointestinal and neuromuscular effects, designated the prodromal syndrome, may occur within minutes or hours after irradiation (Langham, 1967). The symptoms may presage death, but at lower doses they may occur without subsequent radiation-induced death or severe illness. The dose-effect relationships for the prodromal syndrome will be included in Section 1.2.3 on the gastrointestinal tract. However, the prodromal syndrome is not the result of gastrointestinal tract irradiation. It is a parasympathetic neurogenic response and is not secondary to gastrointestinal damage. It can be prevented experimentally by ablation of the central nervous system vomiting center.

1.2.2 Bone Marrow

1.2.2.1 Effects of Low-LET Radiation on Bone Marrow

The effects observed after bone marrow irradiation are the result of killing of blood cell precursors (stem cells) in the marrow (Bond *et al.*, 1965; UNSCEAR, 1982) and may lead to a depletion of all of the mature elements in the blood. The bone marrow is the source of most circulating blood cells, the granulocytes, erythrocytes, and platelets. The response of the peripheral blood elements depends upon their normal turnover time, with the exception of lymphocytes. Lymphocytes are very radiosensitive and die soon after irradiation, undergoing interphase rather than mitotic death like mitotic stem cells. A depletion of lymphocytes is seen within hours after irradiation, whereas the decrease in platelets and granulocytes is delayed for several days and the onset of a decrease in erythrocytes occurs slowly, over weeks. If the depression in peripheral blood cells is too severe, an individual may die from infection because of loss of granulocytes, or hemorrhage because of loss of platelets combined with damage to vasculature. The timing of death coincides with the period of maximum depletion of the granulocytes and platelets (Bond *et al.*, 1965). However, unless the total number of bone marrow stem cells is depressed below a critical level, the numbers of peripheral blood cells will return to normal and the individual will survive. Careful medical support, including antibiotics, transfusions, reverse isolation, or marrow transplants, will enable survival at higher doses.

Sufficient information from total-body irradiation of people is available to estimate a bone marrow dose necessary to kill 50% of those exposed (WASH 1400, 1975). This

information has been updated and reviewed several times since the Reactor Safety Study. Summaries and follow-ups of the serious radiation accidents that have occurred since 1945 were presented at a recent conference (Hubner and Fry, 1980). All types of accidental exposures involving high radiation doses were included, and early effects were documented.

A recent analysis of acute radiation lethality due to failure of the hematopoietic system in rats, mice, dogs, swine, monkeys, and humans resulted in a nonsigmoidal type model for estimating mortality incidences after total-body irradiation (Jones, 1981). If the median lethal dose for a species is known and the bone marrow irradiation is uniform, the mortality can be predicted using formulations based on a power function model. Proper constraints must be used, however, to assure that predicted risks are not greater than one.

The effects of dose, dose rate, and depth dose upon radiation mortality were reviewed recently (Cronkite, 1982). The vagaries of determining depth doses from a fallout field and determining dose protraction factors were noted, as was the conservatism of the NCRP radiation protection guidelines (NCRP 42, 1974) for the medical treatment of exposed populations. A median lethal dose for humans of 3.5 Gy in air for a fallout gamma field and 100% mortality around 5 Gy were given by Cronkite as best "guesstimates" for death from bone marrow injury. The NCRP has estimated the median lethal dose to be about 3.15 Gy to the midpoint of the adult body (NCRP 42, 1974).

The impact of estimates of human radiation tolerance on medical management of radiation emergencies was the topic of another recent paper (Lushbaugh *et al.*, 1982). Estimates of human total-body radiation tolerance were summarized from previous data. New information was presented on radiation doses producing 50% incidence of prodromal symptoms. Some of these doses are relatively low, for example, 0.97 Gy for anorexia. In addition, a model was given for the influence of fractionation of the radiation on death from total-body exposure. The isoeffect relationship for D_{50} is $3.45t^{0.26}$ where 3.45 Gy is the nominal single lethal dose corresponding to a protracted exposure to about 530R of x-radiation over 1 week. Time t (days) is used to adjust the D_{50} for application to exposures longer than 1 day.

Radiation accidents involving total-body exposure were reviewed recently (Baverstock and Ash, 1983). It was hoped that analysis of the data from these accidents would provide improved estimates of the D_{50} for humans. Two accidents, one in the USA, the other in Yugoslavia, were studied in detail, with a re-examination of the dosimetry involved. Differences in symptoms among the patients in the two groups could not be resolved by differences in radiation dose. The conclusion was, in light of the uncertainties and small amount of information available, that "the low-LET radiation dose in bone marrow likely to kill only a few healthy people might be not less than 3 Gy" (Baverstock and Ash, 1983).

Mole (1984) recently used data on total-body exposure of laboratory animals to determine the shape of the dose-effect curve for 60-day lethality and demonstrated the shape to be similar for different mammalian species. Using a shape determined from laboratory animal data and a single point assumed to fall on the true dose-effect curve for humans, derived from data based on exposure of humans, Mole estimated the D_{50} for 60-day lethality, after uniform total-body exposure, to be about 4.5 Gy to the bone marrow. All of the individuals in Mole's data set received some medical treatment. Most were hospitalized. Several received antibiotics and injections of red cells and platelets. Some were isolated with strict aseptic and antiseptic precautions. Although Mole argued that the benefit of medical treatment was overvalued (and therefore that his estimate of a 4.5 Gy LD_{50} was applicable for persons with

minimal medical treatment), our interpretation is that his estimate of an LD_{50} of 4.5 Gy may be appropriate for individuals who received supportive medical treatment.

Data from humans alone are not adequate to determine both the D_{50} and the shape parameter, the effect of medical treatment, or the effect of dose protraction. Therefore, it is necessary to rely on animal data.

The dose-effect curves used for mortality are based on two parameters, a D_{50} and a shape parameter. Data based on exposure of humans are too uncertain to use to estimate the shape of the dose-effect relationship for 60-day mortality. Thus results from exposure of laboratory animals were used. Implied in this approach is the assumption that the shape of the dose-effect curve is the same for the different species considered. Based on available information, this is a reasonable assumption (NCRP 42, 1974; Jones, 1981).

To estimate the shape of the dose-effect relationship for mortality, data have been used from the total-body (bilateral) exposure of dogs to external photon radiation (x-rays) at high dose rates (Michaelson *et al.*, 1968; Hansen *et al.*, 1961). Dogs were selected mainly because their body size is similar to humans. It is widely accepted that the sensitivity, as measured by the D_{50} for mortality from injury to the bone marrow, is correlated with body weight. This is shown in Figure 1.2, based on data obtained from UNSCEAR (1982) for different mammals with the current best estimate of 3.4 Gy for humans added.

The shape parameter V, estimated from data based on studies with dogs, was approximately 10 for minimal treatment. It is our estimate that there is a factor of 1.5 uncertainty in this shape parameter. A detailed discussion of uncertainties is given in section 1.4.

Figure 1.3 shows that the risk estimate for minimal treatment is consistent with available information for 60-day lethality after brief total-body exposure of humans. Also shown is the dose-effect curve for 60-day lethality after brief bilateral exposure of dogs to 1000 kVp x-rays based on reported data (Michaelson *et al.*, 1968; Hansen *et al.*, 1961) used to estimate the shape of the dose-effect relationship for humans.

For supportive and intensive treatment we recommend using a shape parameter of 6.6, the same value used to derive lower bounds for risk with minimal treatment. The value 6.6 is consistent with the very limited available human data (Mole, 1984; Smith, 1983).

1.2.2.2 Dose-Effect Relationship: Mortality

An estimate of the D_{50} for 60-day mortality has been obtained for brief total-body exposure (0-1 days) to external photon irradiation. For minimal medical treatment, a D_{50} of 3.4 Gy is used, as was suggested by the Advisory Committee for the Reactor Safety Study (WASH 1400, 1975), based on a careful review of the available data for exposure of humans. These data are too uncertain to provide reliable information on the shape of the dose-effect curve (Smith, 1983; Baverstock and Ash, 1982). As discussed in the Reactor Safety Study, the D_{50} would be expected to increase in the case of supportive and intensive medical treatment.

1.2.2.3 Influence of Medical Treatment

Three categories of medical treatment are considered: minimal, supportive, and intensive. These are the same three categories as were used in the Reactor Safety Study (WASH 1400, 1975) except that what was called heroic treatment is now called intensive treatment.

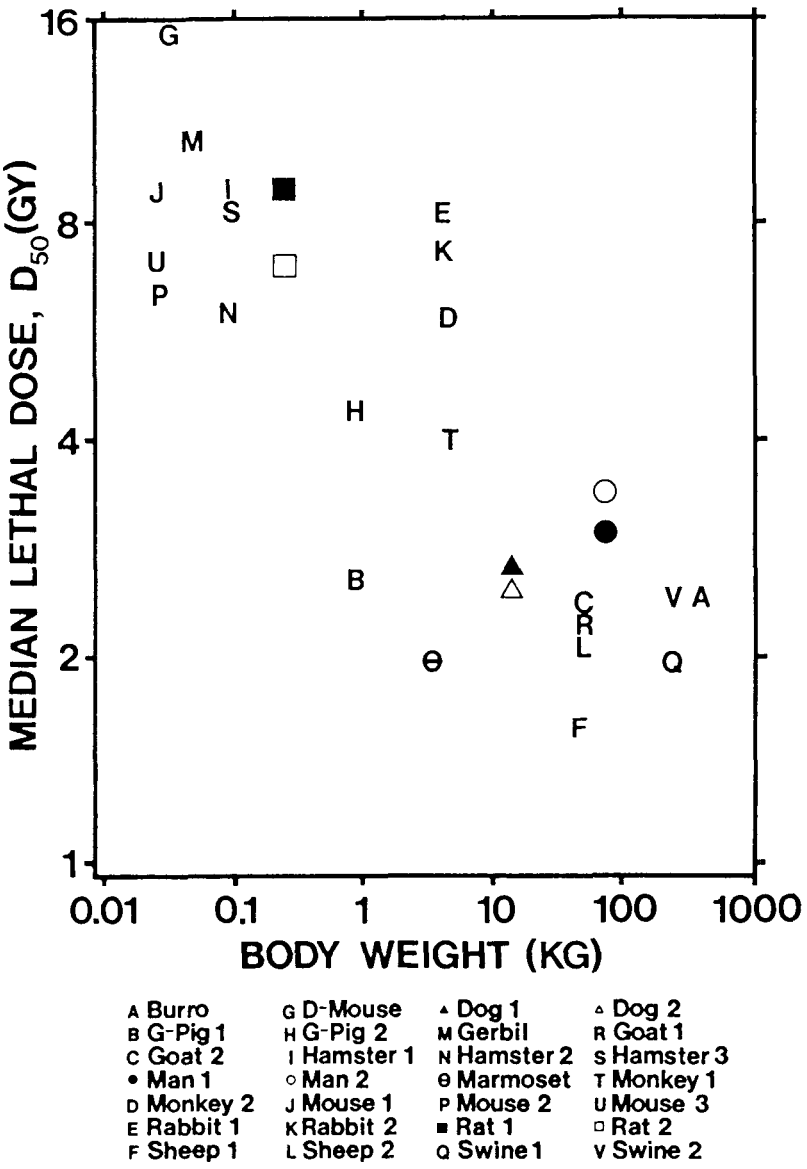

Figure 1.2 Relationship between D_{50} for mortality and body weight for various mammals (UNSCEAR, 1982). A point has been added for humans (based on D_{50} of 3.4 Gy) for brief total-body exposure. Results are for total-body exposure to low-LET radiation.

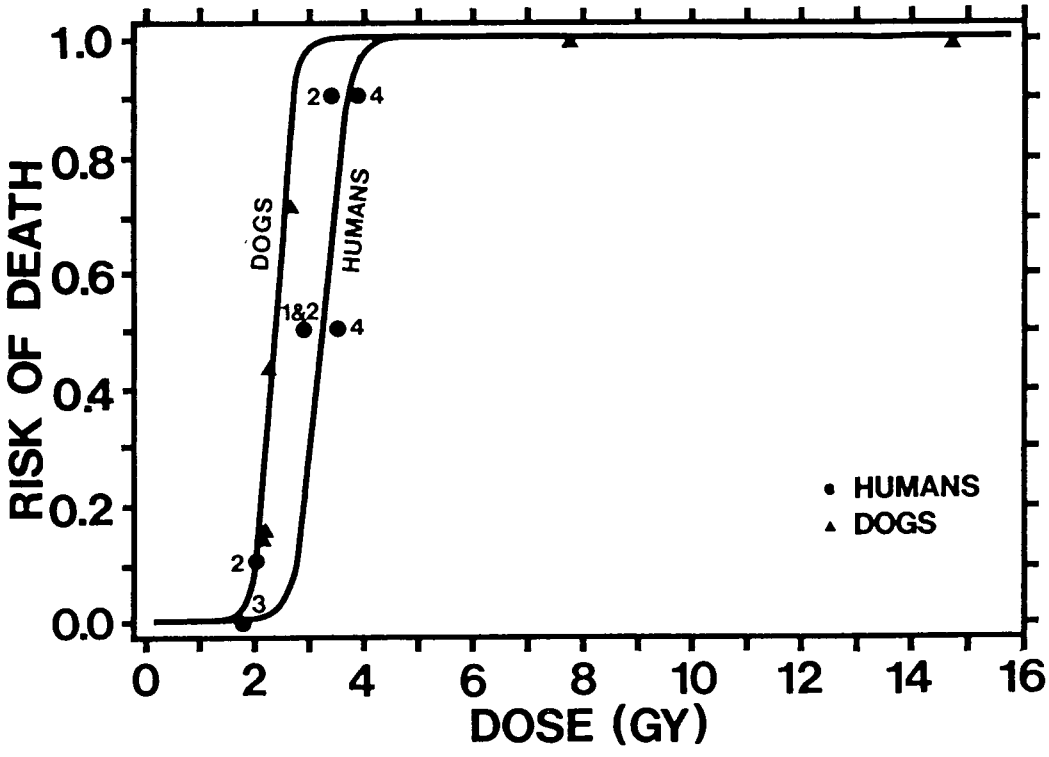

Figure 1.3 Dose-effect curves for early mortality after total-body exposure of dogs and humans to low-LET radiations.

The curve for humans is used to estimate mortality risks associated with brief exposure during the first day after a nuclear power plant accident. Data for dogs are from Michaelson et al. (1968) and Hansen et al. (1961). Origin of data for humans: 1, judgment of NCRP 42 1974 (converted to Gy using conversion factor given in NCRP 42); 2, judgment of Langham 1967 (157, Table 12, assumed to be for normal individuals); 3, Marshall Islanders (protracted exposure); 4, best estimate of the Biomedical and Environmental Assessment Group at Brookhaven National Laboratory (WASH 1400, 1975).

Several publications are available concerning recommended medical treatment for total-body exposure to external radiation as well as for external and internal contamination by radionuclides (Safety Series 47, 1978; ICRP 28, 1978; NCRP 65, 1980).

As in the Reactor Safety Study and for total-body exposure, the term "supportive treatment" indicates procedures such as administration of appropriate antibiotics, blood, and platelet transfusions, and reverse isolation (i.e., measures to protect the patient from pathogenic bacteria and viruses). The term "intensive treatment" indicates, in addition to supportive treatment, extraordinary procedures such as bone marrow transplantation. The term "minimal treatment" indicates the absence of any of these measures. Basic first aid is considered minimal treatment.

Two types of isolation (protective and simple) have been considered for supportive treatment of leukemia patients to reduce the frequency of infection (Nauseef and Maki, 1981; Levine *et al.,* 1973). Levine and coworkers employed protective isolation using an air-filtration facility and a complex prophylactic regimen that included oral, non-absorbable antibiotics. Levine compared the results of this combination of protective isolation and antibiotics with the results obtained using antibiotics alone and with results obtained using neither protective isolation nor antibiotics. Results indicated that both infections and death from infection can be significantly reduced by protective isolation when used in conjunction with antibiotics. Nauseef and Maki (1981) explored the benefits available through use of simple isolation. Simple isolation involves standard precautions to prevent against infection, i.e., the patient is given a private room and persons entering the room are required to wear clean gowns, gloves, and masks. It does not involve complex and expensive procedures such as laminar air flow and high efficiency air filtration devices. The study compared simple isolation with standard hospital care (i.e., neither simple nor protective isolation). Nauseef and Maki were unable to demonstrate any benefit of simple reverse isolation. Neither simple nor protective isolation have been demonstrated to be life-saving from deaths due to infection unless antibiotics and blood are simultaneously administered.

Studies in which dogs were briefly exposed to potentially lethal x-ray doses indicate that supportive treatment can lead to an increase in the median lethal dose by a factor of about 1.5 (Sorensen *et al.*, 1960; Perman *et al.*, 1962). The supportive treatment consisted of the combined use of several antibiotics, whole-blood or platelet-rich plasma transfusions, parenteral fluids, and forced oral feeding of nutritional supplements.

Not everyone agrees that supportive treatment may be life-saving following brief total-body exposure to potentially lethal radiation doses (Mole, 1984). However, based on the studies using dogs (Sorensen *et al.*, 1960; Perman *et al.*, 1962), it was concluded in the Reactor Safety Study (WASH 1400, 1975) that supportive medical treatment following brief total-body exposure to radiation could lead to a factor of 1.5 increase in the median lethal dose to the bone marrow. We believe that, although the specific element or elements of supportive treatment responsible for the effect has not been well estabished, there is a benefit of supportive treatment. Our estimate of the median lethal dose for supportive treatment is 4.5 Gy. This point estimate is slightly lower than the Reactor Safety Study estimate of 5.1 Gy. However, when the uncertainty in the estimate is considered (see section 1.4.2), the change is not large.

Only limited data are available on the impact of intensive medical treatment on mortality risks. Total-body exposure followed by bone marrow transplantation is sometimes used in

the treatment of leukemia and aplastic anemia (Thomas *et al.*, 1975, 1977; Storb, 1981). Cytotoxic drugs are also used and contribute to the depression of bone marrow cells. Patients receive about 1 percent of their normal complement of nucleated bone marrow cells as a transplant. Those for whom the transplant does not take die from septicaemia, resulting from extensive gastrointestinal ulceration. Those who respond to treatment may still die from interstitial pneumonitis or graft rejection, and others may die from recurrent disease.

Available data for 100 leukemia patients treated with 10 Gy total-body doses followed by bone marrow transplantation suggest that about 10 Gy to the bone marrow would lead to a risk of about 20% for 60-day lethality even if bone marrow transplantation is carried out (Thomas *et al.*, 1975, 1977). Of the survivors, approximately 20% develop graft versus host disease and about 10% die from it (Schulman *et al.*, 1978). Therefore the overall risk of death would be about 30%. Several factors make these data difficult to interpret. Typically the patients receiving radiation therapy had failed to respond to intensive chemotherapy. Therefore it is likely their bone marrow was damaged before irradiation. However, they received marrow from perfectly matched donors. Perfect matches might not be possible in the event of a nuclear power plant accident. Finally, the patients were suffering from leukemia, which itself reduces the body's ability to respond to infection. Precise estimates of the D_{50} or the shape of the dose-effect relationship cannot be obtained from these data. However, if a shape parameter of 6.6 is used in conjunction with an LD_{30} of 10 Gy from the data cited above, an estimate of 11 Gy for the LD_{50} is obtained.

Equations (1.4) through (1.6) summarize our recommendations for predicting risk of death from bone marrow syndrome with minimal, supportive, and intensive treatment.

Minimal Treatment

$$\text{Cumulative Hazard} = H_m = ln(2)\,(D/3.4)^{10} \tag{1.4}$$

$$\text{Risk}_m = 1 - \exp\,[-ln(2)\,(D/3.4)^{10}]$$

Supportive Treatment

$$\text{Cumulative Hazard} = H_s = ln(2)\,(D/4.5)^{6.6} \tag{1.5}$$

$$\text{Risk}_s = 1 - \exp\,[-ln(2)\,(D/4.5)^{6.6}]$$

Intensive Treatment

$$\text{Cumulative Hazard} = H_i = ln(2)\,(D/11)^{6.6} \tag{1.6}$$

$$\text{Risk}_i = 1 - \exp\,[-ln(2)\,(D/11)^{6.6}]$$

Risk estimates for each category of medical treatment are given in Figure 1.4. Because they are based on total-body exposure, they may accommodate some interorgan (nonindependent) effects.

1.2.2.4 Protracted Exposure

The risk estimates in equations (1.4) through (1.6) are primarily for brief exposure to external photon radiation during the first day after a nuclear power plant accident. Effects of protracted internal beta exposure over longer times must also be considered. Data for internal low-LET (beta and gamma emitters) exposure of dogs through inhalation or injection of soluble radionuclide forms that mainly irradiate the bone marrow or total body indicate that protraction of the dose over about 30 days or longer led to a median lethal dose of about 10 Gy to the bone marrow delivered within 30 days (McClellan *et al.*, 1982; Scott and Hahn, 1980). Note that the 10 Gy represents a 30-day dose to the bone marrow. Most deaths occurred between about 10 and 30 days after exposure and were caused by injury to the hematopoietic system. Most dogs that survived more than 30 days were able to accumulate very large additional doses without fatal early effects. These results suggest that if supportive treatment for effects of internal radionuclide contamination is to be life-saving, treatment should be started within the first 10 days after exposure to radionuclides that irradiate the bone marrow.

Comparing the median lethal dose of 2.5 Gy for brief bilateral exposure of dogs to external low-LET photon radiation to the 10-Gy median lethal dose for the protracted internal beta dose over 30 or more days suggests a dose-effect modifying factor of $10/2.5 = 4$. Multiplying this factor times the D_{50} for brief external photon exposure in the case of minimal treatment gives a D_{50} for protracted internal beta exposure over 30 or more days, in the case of minimal treatment of 4×3.4 Gy or approximately 14 Gy for humans.

There are no reliable mortality data that allow the derivation of a dose-effect curve for mortality from protracted low-LET beta dose over an intermediate time between the brief 1-day exposure and the 30-or-more-day exposure already considered. However, for protracting the dose over about 14 days, both the multifactor model of Yuhas *et al.* (1972) for human blood cell responses to single or multiple total-body therapeutic radiation exposure and the Los Alamos empirical human lethality model, in which the D_{50} increases with exposure time to the 0.26 power (Lushbaugh *et al.*, 1982) led to a dose rate protraction factor of about 2. Multiplying the D_{50} of 3.4 Gy for brief exposure to low-LET radiation by 2 leads to a D_{50} for protraction of the dose over about 14 days of approximately 7 Gy. All D_{50} values so far derived are summarized in Table 1.1. Values for the shape parameter V are also given. In this report, it is assumed that V is independent of dose rate. As better information becomes available, these estimates could be refined.

Available data are too limited to adequately determine threshold doses for death from irradiation. No research has been conducted with sample sizes large enough to lead to accurate estimates of a threshold dose. Threshold doses cited in the literature may be very imprecise.

Because the deaths caused by large radiation doses occur relatively early, they contribute a great deal to the shortening of the mean survival time for an exposed population. The distribution of times to death depends on dose, dose rate, and cause of death (Sacher and Trucco, 1966; Blair, 1952; Ainsworth *et al.*, 1975; Yuhas, 1969; Scott and Ainsworth, 1980). Information in Table 1.2 can be used in evaluating life shortening effects caused by exposure

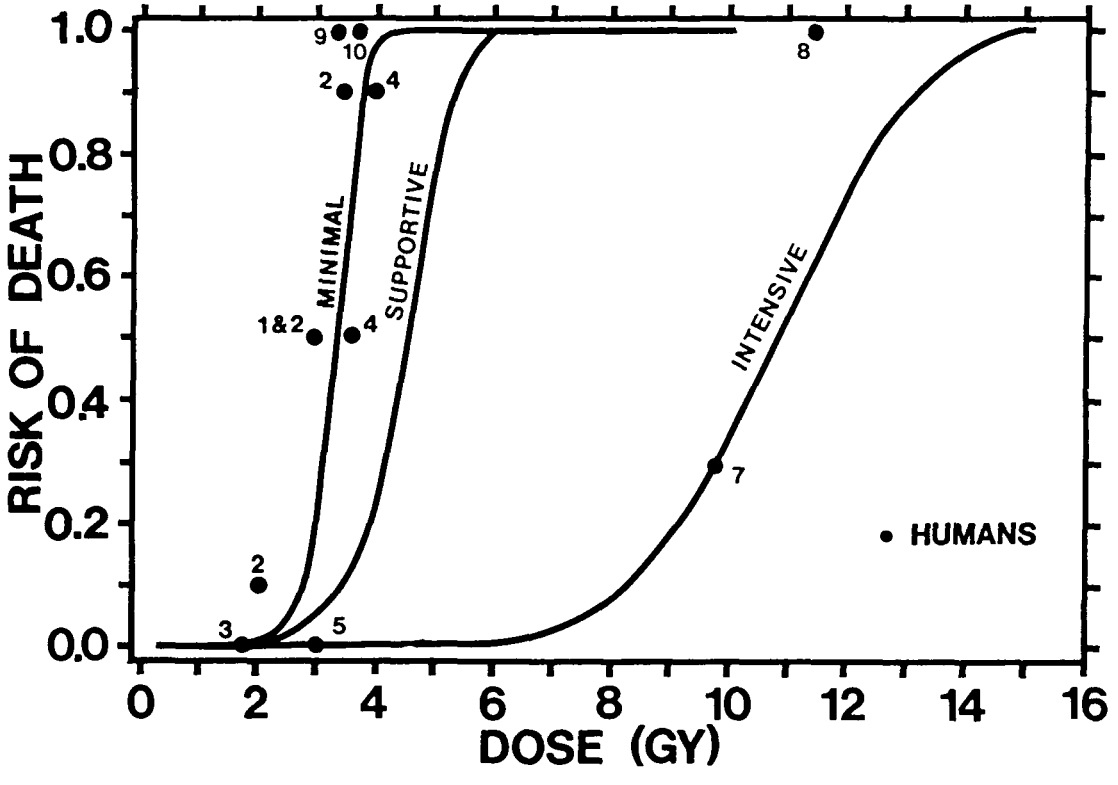

Figure 1.4 Risk estimates for various categories of medical treatment.

Based on same data used in Reactor Safety Study (WASH 1400, 1975). The data for minimal treatment are the same as in Figure 1.3. Origin of the other data: 5, radiation therapy series, 20 patients (Rider and Hasselback, 1968); 7, 100 leukemia patients (Thomas, 1977; Schulman et al., 1978); 8 and 9, accident victims at Los Alamos, 1945 (Hempelman, 1980); 10, accident victim at Vinca, Yugoslavia (Mole, 1984). In addition to these three accident victims who died, there are approximately 30 victims who survived with doses in the range from 0.1 to 4.5 Gy.

Table 1.1 Median Dose Estimate (D_{50}) and Shape Parameter (V) for Early Mortality After Total Body Irradiation when Injury to the Bone Marrow is the Major Cause of Death[a]

Treatment	Parameter	Time Period of Dose Accumulation (days)		
		0 - 1	1 - 14	14 - 30
Minimal	D_{50} (Gy)	3.4[b]	[7[c]]	[14[d]]
	Slope (V)[e]	10	[10]	[10]
Supportive	D_{50} (Gy)	[4.5[f]]	-	-
	Slope (V)[e]	[6.6[g]]	-	-
Intensive	D_{50} (Gy)	[11[h]]		
	Slope (V)[e]	[6.6[g]]	-	-

[a] Brackets indicate that no direct measurements are available from studies of human populations or laboratory animals; estimates were derived from model calculations based upon limited observations made at different total doses and dose rates or using different but related biological endpoints.

[b] Best estimate of Advisory Committee for Reactor Safety Study (WASH 1400, 1975), based on limited data for human exposure to external radiation.

[c] Based on protraction factor of 2 suggested by: (1) multifactoral model of Yuhas et al. (1972) for human blood cell responses to single or multiple whole-body therapeutic radiation exposure; (2) Los Alamos empirical human lethality model derived from data for human exposure where D_{50} increases as exposure to the 0.26 power (cited from Lushbaugh et al., 1982).

[d] Based on protraction factor of 4 suggested by: (1) multifactoral model of Yuhas et al. (1972) for human blood cell responses; (2) 60-day lethality data for dogs after brief total-body external x-ray exposure (Michaelon et al., 1968; Hansen et al., 1961) when compared to that for protracted internal beta exposure (Hahn et al., 1979; McClellan et al., 1982).

[e] Best estimate derived from 60-day lethality data after single whole-body bilateral exposure of dogs to x-rays (Michaelson et al., 1968; Hansen et al., 1961). Can be assumed to be independent of dose rate as was observed for case of lung irradiation.

[f] Based on humans that received supportive treatment. This value is based on the same data reviewed by Mole (1984). As indicated in the text, although Mole recommends 4.5 Gy as the LD_{50} for minimal treatment, we believe that it may be appropriate for supportive treatment.

[g] A subjective estimate that is consistent with the available human data (Mole, 1984; Smith, 1983; Hubner and Fry, 1979).

[h] Based on 30% mortality incidence after 10 Gy exposure of human leukemia patients (Thomas et al., 1978; Schulman et al., 1978). D_{50} can be estimated assuming slope is same as for supportive treatment.

Table 1.2 Relationship Between Total Body Dose and Survival Time for Those Receiving Lethal Injury After Brief or Protracted Exposure (Assuming only minimal treatment)

Type of Exposure	Dose Range (Gy)	Likely Time to Death (Days)
Brief	> 4[a]	< 14
	2-4[a]	< 60
	< 2[b]	No deaths from early effects
Protracted[e]	> 8[c]	10-90
	< 7[d]	No deaths from early effects

[a]Based on atomic bomb survivors (UNSCEAR, 1982; Okita, 1975)

[b]Based on 4 individuals exposed in the Argonne criticality accident to total body doses less than about 1.6 Gy (Hasterlik and Marinelli, 1955). None died from early effects even though only bed rest was used as treatment while in the hospital.

[c]Based on dogs exposed via inhalation or injection of beta-emitting radionuclides in soluble forms (McClellan et al., 1982). A cross-species extrapolation factor of 3.4/2.5 = 1.36, based on the ratio of the acute D_{50} for the two species was multiplied times the 6 Gy value obtained from the data for dogs.

[d]Based on 23 Japanese fisherman exposed to the same radioactive cloud as the Marshall Islanders. Their estimated total body dose was less than 7 Gy (Kumatori et al., 1980).

[e]Protracted dose from internally deposited fission product radionuclides.

to radiation from a nuclear power plant accident.

1.2.2.5 Sensitive Subgroups

An important consideration is whether the risk estimates given in equations (1.4) through (1.6) would be adequate for sensitive subgroups. Only limited data are available upon which to make such a decision. In Figure 1.5 are shown estimates of the median lethal doses for various species (UNSCEAR, 1982). Where more than one value was available for the species, notations such as dog1 and dog2 have been used to indicate these different values. Note that for species of similar body weights the variability in the median lethal dose is relatively small.

It is reasonable to assume that variability within a single species would be less than that for different species of similar sizes. For different species of similar sizes (based on body weight), the median lethal dose varies by less than a factor of 2. See, for example, the values for human, monkey, dog, burro, goat, swine, and sheep in Figure 1.5.

Data for individuals with inoperable cancer or terminal leukemia with total-body doses (midline doses) between 0.3 and 3 Gy can be used to derive a plausible lower bound for the median lethal dose (Lushbaugh *et al.*, 1967). Because of their advanced malignant disease, these patients had a relatively high probability of dying even without radiation exposure. From these data, an estimate of a median lethal dose of 2.8 Gy is derived, which is a factor of $3.4/2.8 = 1.2$ times less than our best estimate of the median lethal dose for healthy individuals.

An analysis was conducted to determine the possible impact of sensitive individuals in the population on the D_{50} for lethality from injury to the hematopoietic system. Assuming that the D_{50} for sensitive individuals was no smaller than the 2.8 Gy obtained for very sick individuals, one can make judgements about the effect of sensitive individuals on the D_{50} for a mixed population. A conservative estimate of a 10% composition of sensitive individuals in a general population was derived in the German Nuclear Power Station Risk Study (1981). Assigning 10% of the population a D_{50} of 2.8 Gy, and the remaining 90% a D_{50} of 3.4 Gy, changes the D_{50} by only about 4% when a constant shape factor of 10 is used. Considering the range of uncertainty in the shape parameter, and allowing for variation in the D_{50} due to supportive medical treatment, the D_{50} for the mixed population would be expected to differ from that for normal healthy individuals by less than 10%. Of course, the presence of sensitive individuals would be more important in the region of the dose-response curve below the LD_{50}. Nonetheless, the presence of sensitive individuals in the population should not contribute much to the overall uncertainty in the assessment of early mortality. A detailed discussion of uncertainty is provided in section 1.4.

1.2.3 Gastrointestinal Tract

1.2.3.1 Early Radiation Effects

Early radiation effects resulting in illness or death can be induced in the gastrointestinal tract after total-body irradiation or ingestion of fission product radionuclides. Two syndromes induced are the prodromal and the gastrointestinal. No human incidents have ever resulted in the ingestion of sufficient quantities of radionuclide to result in illness. Effects have been seen,

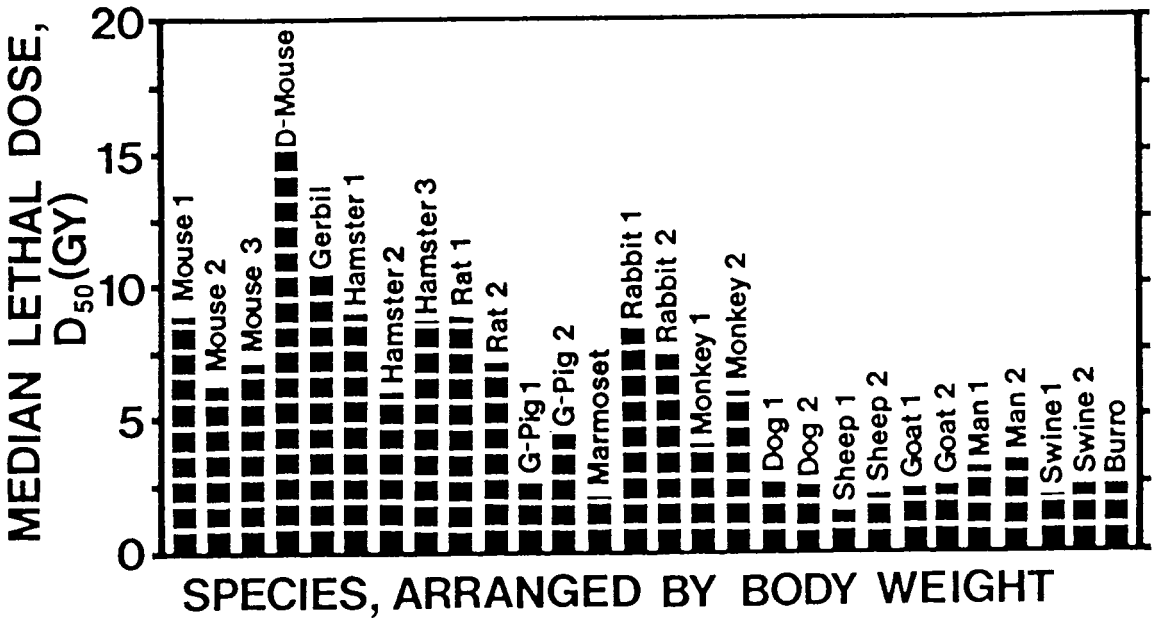

Figure 1.5 Bar graph of D_{50} (Gy) versus species arranged according to body weight (UNSCEAR, 1982).

however, in experimentally exposed laboratory animals.

The prodromal syndrome is a group of symptoms and signs of acute gastrointestinal and neuromuscular effects that begin to occur within hours after irradiation. The gastrointestinal symptoms include anorexia, nausea, vomiting, and diarrhea. The neuromuscular symptoms include fatigue, listlessness, fever, and hypotension followed by hypotensive shock. At the median lethal dose, the principal symptoms of the prodromal reaction are anorexia, nausea, vomiting, and fatigue. Diarrhea, fever, and hypotension seem to be signs of supra-lethal doses (Langham, 1967). Prodromal symptoms can occur without subsequent radiation-induced death or severe illness (Andrews *et al.*, 1980; Baverstock and Ash, 1983). The time of onset, severity, duration, and recovery vary according to the magnitude of the dose, dose rate, and region of the body irradiated.

The prodromal syndrome is the result of a parasympathetic neurogenic response to irradiation. The symptoms can be produced by exposures of the abdomen, thorax, or head. Irradiation of the upper mid-portion of the abdomen (over the stomach) elicits the responses with the least dose, whereas irradiation of the extremities is ineffectual. Shielding the abdomen during total-body irradiation can prevent the response unless large doses are delivered simultaneously to the head. Whether or not a radiation dose delivered from an ingested beta-emitting radionuclide (for example, following inhalation exposure) would induce prodromal symptoms is conjectural. No reliable data for internal emitters are available to make these estimates.

1.2.3.2 Dose-Effect Relationship: Morbidity

Dose-effect relationships for prodromal vomiting were developed in the Reactor Safety Study (WASH 1400, 1975). Since then, dose-effect information for other prodromal symptoms has been developed (Lushbaugh *et al.*, 1982). The information is based on a retrospective study of 2000 patients given therapeutic total-body irradiation. Estimates of the median effective doses for brief exposures ($<$ 1 day) are given in Table 1.3 for the symptoms of anorexia, nausea, fatigue, vomiting and diarrhea. The D_{50} was lowest for anorexia, 0.97 Gy, and highest for diarrhea, 2.3 Gy. The median effective doses for protracted exposures (1-7 days) for each symptom are also given in Table 1.3. The protraction of the dose increases the median effective dose by a factor of 1.9 to 2.7, depending on the effect.

A dose-effect relationship for prodromal vomiting after brief exposure is shown in Figure 1.6 and is mainly based on the same data used in the Reactor Safety Study (WASH 1400, 1975). The median effective doses reported by Lushbaugh (1982) for anorexia, nausea, fatigue, and diarrhea were added to the figure.

Estimates of the shape parameter V are also summarized in Table 1.3. These are based on information from Lushbaugh (1969, 1982), Langham (1967), and the Reactor Safety Study (WASH 1400, 1975). It is our recommendation that only the most serious effects (diarrhea and vomiting) be included in the final accident consequence models.

1.2.3.3 Dose-Effect Relationship: Mortality

Results of bone marrow transplantation studies of Thomas *et al.* (1975) indicate that, in the absence of hematological complications, the human total-body dose for fatality from gastrointestinal injury is above 10 Gy. However, no reliable data based on exposure of humans

Table 1.3 Median Dose Estimates (D_{50}) and Response Curve Slopes (V) for Prodromal Symptoms After Total Body Irradiation

Symptom	Parameter[a,b]	Time Period of Dose Accumulation (Days)	
		0-1	1-7[c]
Anorexia	D_{50} (Gy)	0.97	2.0
	V	2	[2]
Nausea	D_{50} (Gy)	1.4	2.6
	V	2	[2]
Fatigue	D_{50} (Gy)	1.5	Not Determined
	V	2	[2]
Vomiting	D_{50} (Gy)	1.8	4.9
	V	3	[3]
Diarrhea	D_{50} (Gy)	2.3	5.3
	V	2	[2]

[a] Midline, midplane upper abdominal doses.

[b] D_{50} estimates of Lushbaugh (1982), based on retrospective study of 2000 patients given total body irradiation, exposure rates greater than 30 R/day. Based on data from Figure 3.7, the shape parameter, V, was estimated to be approximately 3 for vomiting. Shape parameter estimates for anorexia, nausea, fatigue and diarrhea were based on D_{50} estimates from the table and D_{10} (dose which affects 10%) estimates from Lushbaugh (1969) and Langham (1967), where:

$$V = 1.884/\ln(D_{50}/D_{10})$$

[c] Brackets indicate that values are assumed to be the same as those for the 0-1 day period.

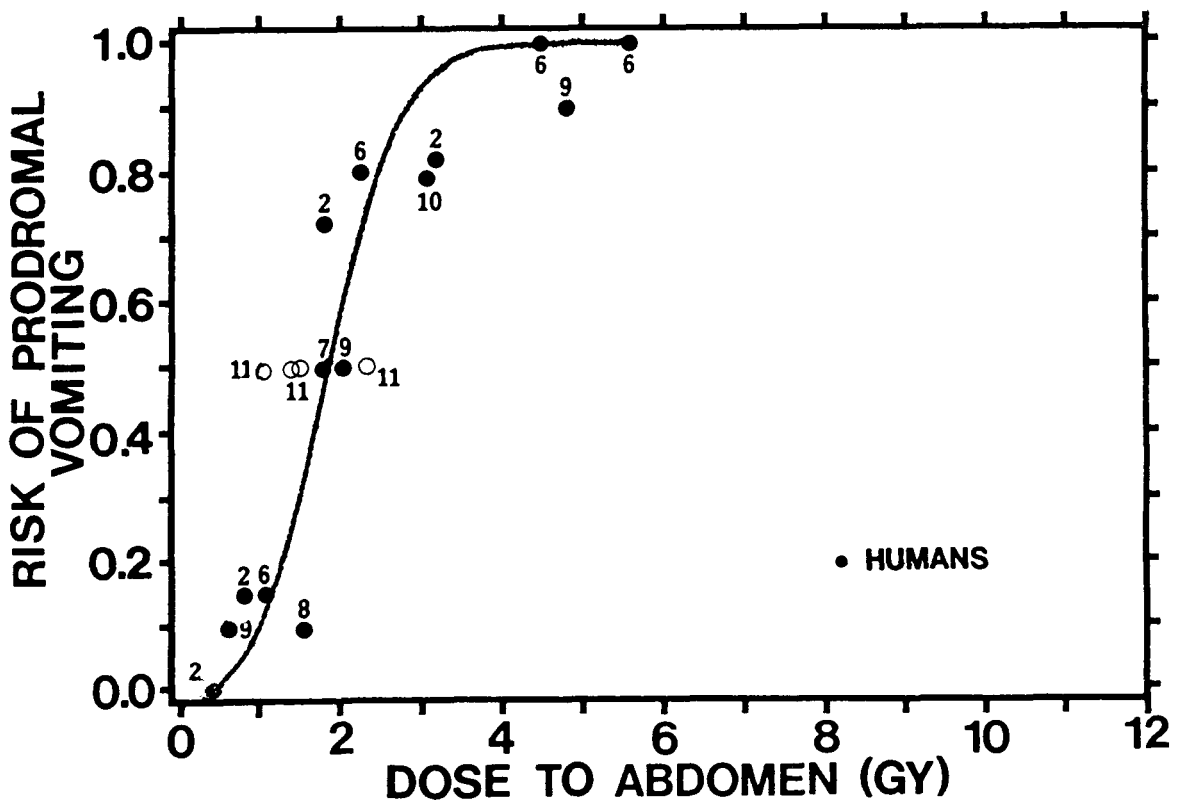

Figure 1.6 Dose-effect relationship for prodromal vomiting within 2 days.

Based on information provided in the Reactor Safety Study (WASH 1400, 1975) with additional data from Lushbaugh (1982), based on 2000 patients given therapeutic total-body irradiation. The median effective doses given by the open circles, #11, represent from left to right anorexia, nausea, fatigue, vomiting, and diarrhea. Origin of other data: 2, Langham (1967), accident exposure cases; 6, accident exposure cases (Thomas and Wald, 1959; updated); 7, therapy patients (Thomas, 1971); 8, Ronglap fallout cases, protracted 50-hour exposure (Langham, 1967); 9, half the difference between normal arithmetical and log-normal values given in Langham (1967); 10, Toronto-therapy cases (11/14) with Gravol pre-treatment.

are available for use in developing a dose-effect relationship for mortality caused by injury to the gastrointestinal tract. Data based on exposure of laboratory animals were used to arrive at dose-effect relationships. Because different mammals of a similar age category respond in a similar way to irradiation of the gastrointestinal tract, this is a reasonable approach (Bond, 1965; Maisin *et al.*, 1971). Parameters for estimating mortality risks are summarized in Table 1.4. The resulting dose-effect relationships are plotted in Figure 1.7. The information on which they are based is discussed below.

For brief exposure, the critical organ is the small intestine. Results of a study, in which the intestines of rats were irradiated outside the body, were used to arrive at a dose-effect relationship for brief exposure (Sullivan *et al.*, 1959). This leads to a D_{50} estimate of 15 Gy to the small intestine. This estimate is applicable for brief high dose rate exposure. It is consistent with the observations in the bone marrow transplantation studies of Thomas *et al.* (1975).

For protracted internal beta exposure, a median lethal dose of 35 Gy to critical cells in the colon was used. The estimate is based on internal exposure of rats and dogs to beta radiation (Cross *et al.*, 1978). The dose-effect curve was assumed to have the same shape (that is, $V = 10$) as was observed for brief exposure. The colon is considered the most critical component of the gastrointestinal tract for internal protracted exposure because the radioactive contaminant remains there longer than in other parts of the gastrointestinal tract (Sullivan *et al.*, 1978). Most of the dose to the colon from a single ingestion will be delivered within 7 days (WASH 1400, 1975) so that doses need not be calculated beyond 7 days. However, if there are situations leading to continued ingestion, this choice of a 7-day dose truncation period may need to be reexamined.

There is evidence, based on studies with laboratory animals, that indicates age at exposure could also be an important variable. In rats, the D_{50} for suckling, weanling, and adult animals for beta radiation from ^{106}Ru-^{106}Rh given by gavage was 55, 670, 330 MBq/kg, respectively (Sullivan *et al.*, 1978). In previous studies with ^{141}Ce (Inaba and Lengemann, 1972) and with ^{95}Nb (Mraz and Eisele, 1977), as well as with the actinides (Sullivan *et al.*, 1978), in neonatal animals there were indications that the radionuclides ^{106}Ru-^{106}Rh were absorbed into the epithelial cells of the mucosa in the small intestine. These results suggest that the D_{50} for lethality could vary by as much as a factor of 670/55, or approximately 10, with age. However, this does not take into consideration that, in neonatal animals the radionuclides enter the epithelial cells and may lead to greater absorbed doses than if passage through the gastrointestinal tract were as rapid as in the adults. From this point of view, the reduced concentrations of radionuclides required for death in the suckling rats may be associated with a larger cumulative radiation dose. And thus the influence of age is more on dose than on sensitivity. If possible, some special considerations should be given to the dosimetry problem with neonates. Available information is too limited to determine threshold doses. Information provided in Table 1.5 can be used to evaluate life-shortening due to effects caused by irradiation of the gastrointestinal tract.

Potish (1980) suggested that certain classes of individuals are more susceptible to intestinal irradiation, including persons with multiple abdominal surgeries, diabetes, vascular diseases, and pelvic inflammatory disease. He also suggested that the sensitivity of an individual to irradiation of the gastrointestinal tract may differ for males and females and is influenced by certain drugs. However, available data are not sufficient to derive dose-effect

Table 1.4 Median Dose Estimates (D_{50}) and Response Curve Slopes (V) for Mortality from Injury to the Gastrointestinal Tract After Exposure to Low-LET Radiation[a]

Critical Organ	Parameter	Time Period of Dose Accumulation (Days)	
		0-1	1-7
Small Intestine	D_{50} (Gy)[f]	15[b]	35[d]
	Slope (V)[b]	10[b]	[10[b]]
Colon	D_{50} (Gy)[f]	[15]	35[c]
	Slope (V)	[10[e]]	[10[e]]

[a]Brackets indicate that no direct measurements are available from studies of human populations or laboratory animals; estimates were derived from model calculations based upon limited observations made at different total doses and dose rates or using different but related biological endpoints.

[b]Based on exteriorized exposure of rat intestines (Sullivan et al., 1959). The bone marrow transplantation studies of Thomas et al., (1975) indicated that in the absence of hematological complications, the human total body dose for producing early mortality from gastrointestinal injury is above 10 Gy.

[c]Based on data for internal exposure of rats to beta radiation from ^{106}Ru-^{106}Rh (Sullivan et al., 1978). Is consistant with exposure time to the 0.26 power dependence of D_{50} predicted by Los Alamos human lethality model (cited from Lushbaugh et al., 1982): leads to dose rate protraction factor of approximately 2 for a 7-day exposure when compared to a 1-day exposure.

[d]Assumed to be approximately equal to value for colon.

[e]Assumed to be same as for brief exposure.

[f]Administration of a mild laxative (supportive treatment) should reduce the dose received by a factor of 2 to 4. Mathematically, this is equivalent to raising the D_{50} by a factor of 2 to 4.

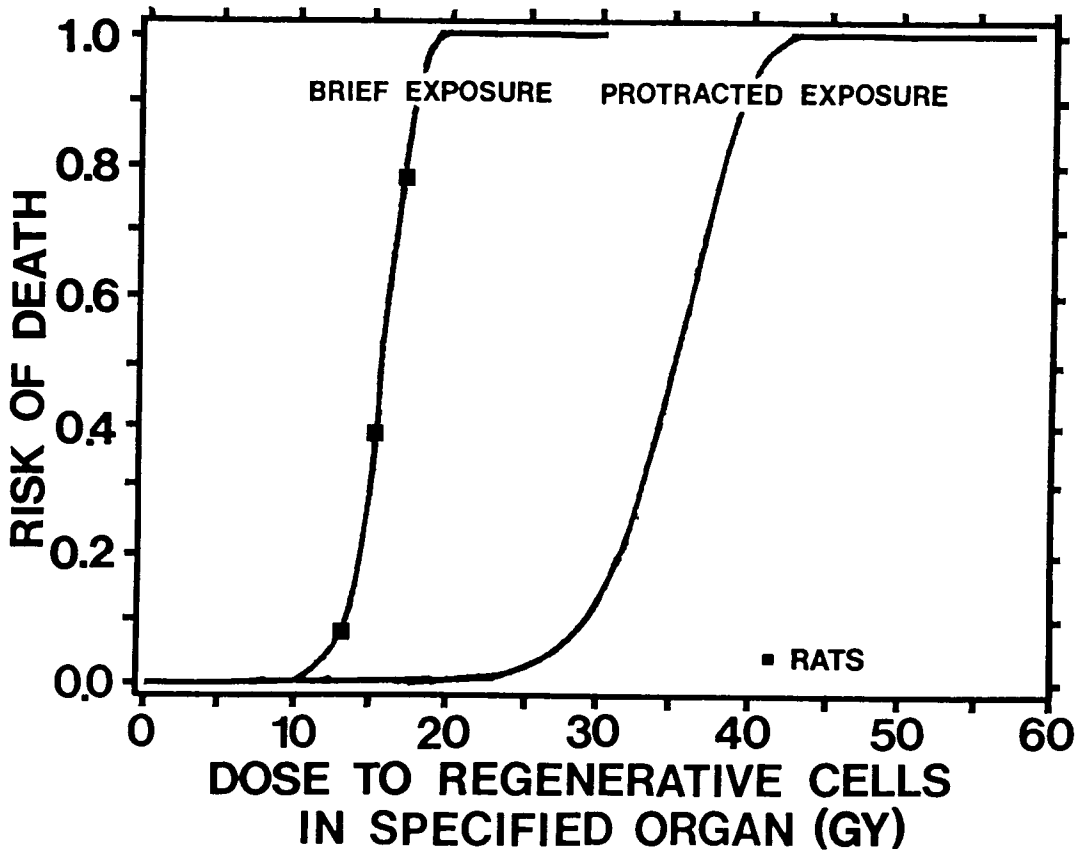

Figure 1.7 Dose-effect relationships for lethality caused by injury to the gastrointestinal tract.

The curve for brief exposure is based on data from Sullivan et al. (1959) for exteriorized exposure of the intestines of rats. The curve for protracted beta exposure is based on rats and dogs exposed to internal beta radiation from ^{106}Ru - ^{106}Rh (Sullivan et al., 1978). A conversion factor of 35 Gy per 330M Bq/Kg was used to obtain the dose in Gy to critical cells.

Table 1.5 Relationship Between Dose to Critical Cells in the Gastrointestinal Tract and Likely Survival Time for Those Individuals Receiving Lethal Injury After Exposure to Low-LET Radiation

Type of Exposure	Estimated D_{50} (Gy)	Likely Time to Death (Days)
Brief	15[a]	< 10[b]
Protracted	35[c]	<180[d]

[a]Based on exteriorized exposure of rat intestines (Sullivan et al., 1959)

[b]Based on dogs, rats, and mice (Bond et al., 1965)

[c]Based on rats receiving intragastric (i.e. directly into the stomach) exposure to ^{106}Rh-^{106}Ru (Sullivan et al., 1978)

[d]Based on dogs receiving intragastic exposure to ^{106}Ru-^{106}Rh.

relationships for these subgroups.

1.2.4 Lungs

1.2.4.1 Early Radiation Effects

Early radiation effects can be induced in the lungs with sufficiently high radiation doses. Irradiation may be the result of total-body exposure, partial body exposure, or exposure from an inhaled beta-emitting radionuclide. However, because of the large radiation doses required to induce disease, no early fatalities of adults from pulmonary injury would be expected after total-body irradiation. However, children may be more sensitive to injury of the lungs. Pulmonary injury may also be of concern if large amounts of radionuclides are inhaled as a result of a reactor accident.

The changes in the lung, radiation pneumonitis and pulmonary fibrosis, are generally the same, regardless of the mode of radiation exposure and are generally divided into three chronologic phases based on acute exposure. The early phase occurs up to about 2 months after irradiation, the intermediate phase from 2 to 9 months, and the late phase after 9 months (Gross, 1977). Initially the alveolar lining and capillary endothelial cells are damaged resulting in increased capillary permeability, edema and accumulation of inflammatory cells. Later, fibrosis of the alveolar septa predominates (Gross, 1981). Chronic occlusive pulmonary vascular lesions were more prominent in dogs exposed to inhaled beta emitters, than animals exposed briefly to external radiation (Slauson *et al.*, 1976, 1977). The severity of reactions and their time course are thought to depend on total radiation dose (Collis and Steel, 1982; Phillips and Margolis, 1972), dose rate (Travis *et al.*, 1983; Depledge and Barrett, 1982), and type of radiation (Mauderly *et al.*, 1980). In one recent study of people briefly exposed to a single dose of x-radiation, the onset of pneumonitis was between 1 and 7 months after irradiation with no correlation between time of onset and radiation dose to the lung over a range of 6.5 to 12.5 Gy (Van Dyk *et al.*, 1981). Other contributing factors to radiation pneumonitis may be underlying infection, age at exposure, or atherosclerosis, but there are no quantitative human data supporting these points (Gross, 1977).

Three therapeutic modalities have been advocated for radiation pneumonitis: corticosteroids, antibiotics, and anticoagulants (Gross, 1977). Only corticosteroid treatment has much success and then only with acute radiation pneumonitis. For inhaled radionuclides, lung lavage is a way to reduce the radiation dose accumulation in the lung by reducing the lung burden of radionuclide. Lavage, in conjunction with chelation therapy, has been used in laboratory animals to reduce the body burden of an inhaled radionuclide by as much as 50% (Muggenburg *et al.*, 1975).

Morbidity effects of exposure of the lung to non-lethal beta-radiation doses have been demonstrated by Mauderly and coworkers (1973) using pulmonary function measurements in dogs. The dogs were exposed via inhalation to ^{90}Y in an insoluble aerosol. The dose was delivered over about two weeks. Functional measurements were taken under the stresses of treadmill exercise and added external respiratory deadspace. Early functional impairments observed included defects in the distribution of ventilation and alveolar-capillary gas exchange. The smallest dose to the lung that was observed to cause alteration in lung function was 49 Gy, approximately one-half of the median lethal dose.

A similar relationship between the dose for morbidity and the dose for lethality was indicated in a second study (Mauderly *et al.*, 1980) in which dog lungs were irradiated over many months by the beta emitter ^{144}Ce, which was inhaled in an insoluble aerosol. In that study, all dogs would have eventually accumulated lethal doses had they not been sacrificed. Dogs sacrificed with cumulative doses of about one-half the median lethal dose were functionally impaired. Observed lesions at sacrifice consisted of widely scattered foci of chronic interstitial pneumonia with an increased number of alveolar macrophages. Results of the studies indicate that dose required to cause morbidity may be about one-half those required for lethality.

1.2.4.2 Dose-Effect Relationship: Brief Exposure

Some clinical data are available on the effects of brief photon irradiation of human lungs. With information about how much dose given in fractions is required for a given level of effect, an equivalent amount of dose for a single exposure can be calculated with a standard procedure. The single dose arrived at in this way is called the nominal standard dose (UNSCEAR, 1982; Ellis, 1969; Cohen, 1966) and is expressed in units of ret (rads equivalent therapeutic). One Gy is equivalent to 100 ret. Based on radiation therapy data, Phillips and Margolis (1972) have estimated a dose of 9 Gy (900 ret) for 5% incidence of radiation pneumonitis and 10.4 Gy (1040 ret) for 50% incidence. A total lung dose of 7 Gy (700 ret) should cause no measurable changes (UNSCEAR, 1982).

Van Dyk *et al.* (1981) provide the most reliable dose-effect information for lethality from radiation pneumonitis in humans after brief exposure to external photon radiation delivered at high dose rates to the upper body. Fitting the cited data using equation (1.1) leads to a sigmoidal curve, with incidences of pneumonitis of 5% and 50% at doses of 6.7 $\pm$ 1.4 Gy and 9.5 $\pm$ 0.7 Gy, where the uncertainties are standard deviations. Most of these individuals died from pneumonitis, therefore the pneumonitis incidence data are used as estimates of mortality risks. Van Dyk *et al.* (1981) fitted the data with a probit model and arrived at a similar estimate of 9.3 Gy for the D_{50}. This suggests that the D_{50} estimate is relatively independent of modeling assumptions because of the steepness of the dose-effect curve. There is more concern about the uncertainty in the shape of the dose-effect curve than in its D_{50}. Data based on exposure of laboratory animals were used to determine the shape of the dose-effect curve for mortality and the impact of protracted internal beta irradiation. Parameters derived for the dose-effect relationships are given in Table 1.6.

A D_{50} of 9.5 Gy is used for mortality from brief exposure during the first day. It is based on results of exposure of humans. The value for the shape parameter V was 4 and is the average value derived from data for brief external x-ray exposure of rats and protracted internal (beta-radiation) exposure of dogs.

1.2.4.3 Dose-Effect Relationship: Protracted Exposure

A second mode of exposure to be considered is protracted internal radiation exposure from inhaled beta-emitting radionuclides. Only limited data are available on early-occurring effects of inhaled radionuclides in humans. The development of radiation pneumonitis, presumably caused by inhalation of radon and radon decay products, was reported for a worker (WASH 1400, 1975), but no reliable dose calculation could be made. Data for lethality in dogs after inhalation exposure to insoluble beta emitting aerosols have, therefore, been used to develop mortality risk estimates for humans (McClellan *et al.*, 1982). Beagle dogs were

Table 1.6 Median Dose Extimates (D_{50}) and Response Curve Slopes (V) for Early and Continuing Effects of Irradiation of the Lungs in Adults[a]

Category	Treatment[h]	Parameter	Time Period of Dose Accumulation (days)			
			0-1	1-14	14-200	200-365
Mortality	Minimal	D_{50} (Gy)	9.5[b]	94[c]	220[d]	540[e]
		Slope (V)	4.0[f]	4.0[f]	4.0[f]	4.0[f]
Morbidity	Minimal	D_{50} (Gy)	4.8[g]	[94[g]]	[110[g]]	[270[g]]
		Slope (V)	4.0[f]	[4.0[f]]	[4.0[f]]	[4.0[f]]

[a] Brackets indicate that no direct measurements are available from studies of human populations or laboratory animals; estimates were derived from model calculations based on limited observations made at different total doses and dose rates or using different but related biological endpoints. For children D_{50} values should be divided by 2.

[b] Based on pneumonitis in humans (Van Dyk et al., 1981).

[c,d,e] Based respectively on dogs exposed via inhalation to beta emitters ^{90}Y, ^{91}Y, and ^{144}Ce inhaled in an insoluble matrix (Scott, 1984; McClellan et al., 1982). Most of the ^{90}Y dose was delivered within about 14 days, the ^{91}Y dose within about 200 days, and the ^{144}Ce dose over times much longer than 200 days.

[f] Average value for rats after thoraxic exposure to x-rays (Dunjic et al., 1960) and for dogs exposed via inhalation to ^{90}Y, ^{91}Y, and ^{144}Ce (Scott, 1984; McClellan et al., 1982).

[g] Only half as much dose is required for morbidity as for mortality (Mauderly et al., 1973, 1980).

[h] Lung lavage, an intensive treatment, can reduce the internal dose to the lungs by a factor of about 2. Mathematically, this is equivalent to raising the D_{50} by a factor of 2.

exposed by inhalation to ^{90}Y, ^{91}Y and ^{144}Ce inhaled in an insoluble matrix. For dogs exposed to ^{90}Y, the radiation dose was protracted over about 2 weeks; over about 200 days with ^{91}Y, and over longer times with ^{144}Ce. New dose-effect relationships (Scott and Seiler, 1984) have been based on these data and on data for brief upper-body exposure of dogs and rats. The dose-effect curves for brief and protracted exposure are shown in Figure 1.8.

Muggenburg *et al.* (1977) have demonstrated in dogs that multiple lung lavage along with chelation therapy can reduce dose to the lung from inhaled insoluble radionuclides by a factor of 2. Because of this reduction, doses to the lung used in the evaluation of risk should be divided by a factor of 2 when intensive medical treatment is considered.

Available information suggests that age at exposure can influence the effectiveness of the radiation exposure (McClellan *et al.*, 1982). About half as much dose was required to the lung of immature dogs as for young adults to cause death from pulmonary injury after inhalation exposure to a beta-emitting radionuclide. Based on these data, values for the D_{50} in Table 1.6 should be divided by 2 for children. This gives a value of about 5 Gy to the lung for the D_{50} for resultant mortality after brief exposure of children indicating that the lung should not be disregarded as a critical organ as has been suggested in the Reactor Safety Study (WASH 1400, 1975).

Because of the limitations of the available data, threshold doses cannot be determined with certainty. Information in Table 1.7 can be used in evaluating life-shortening due to effects caused by irradiation of the lungs.

1.2.5 Thyroid

1.2.5.1 Effects of Low-LET Radiation on the Thyroid

Irradiation of the thyroid can lead to early and continuing effects that include acute radiation thyroiditis, chronic lymphocytic thyroiditis, and hypothyroidism. A detailed discussion of these effects, their relationship to radiation dose, and their association with benign and malignant thyroid diseases is given in Appendix A, Thyroid Effects.

Acute radiation thyroiditis generally occurs within two weeks after exposure to radiation and is characterized by inflammation and necrosis of thyroid tissue. The symptoms are usually mild; however, significant systemic symptoms have occasionally been noted after release of large amounts of stored thyroid hormone.

Chronic lymphocytic thyroiditis is an inflammation of the thyroid that occurs years after radiation exposure. The predominance of lymphocytes in the lesion is suggestive of an autoimmune phenomenon. The significance of this possible sequela is probably not great unless the inflammation is associated with hypothyroidism or benign thyroid nodules. As noted in Appendix A, the risk estimates for hypothyroidism and for benign thyroid nodules thus would include the clinically significant manifestations of chronic thyroiditis.

Hypothyroidism is a deficiency in thyroid function and activity. Signs of hypothyroidism are generally noted within a few years after radiation exposure, but they may be so mild as to be detected only by biochemical tests.

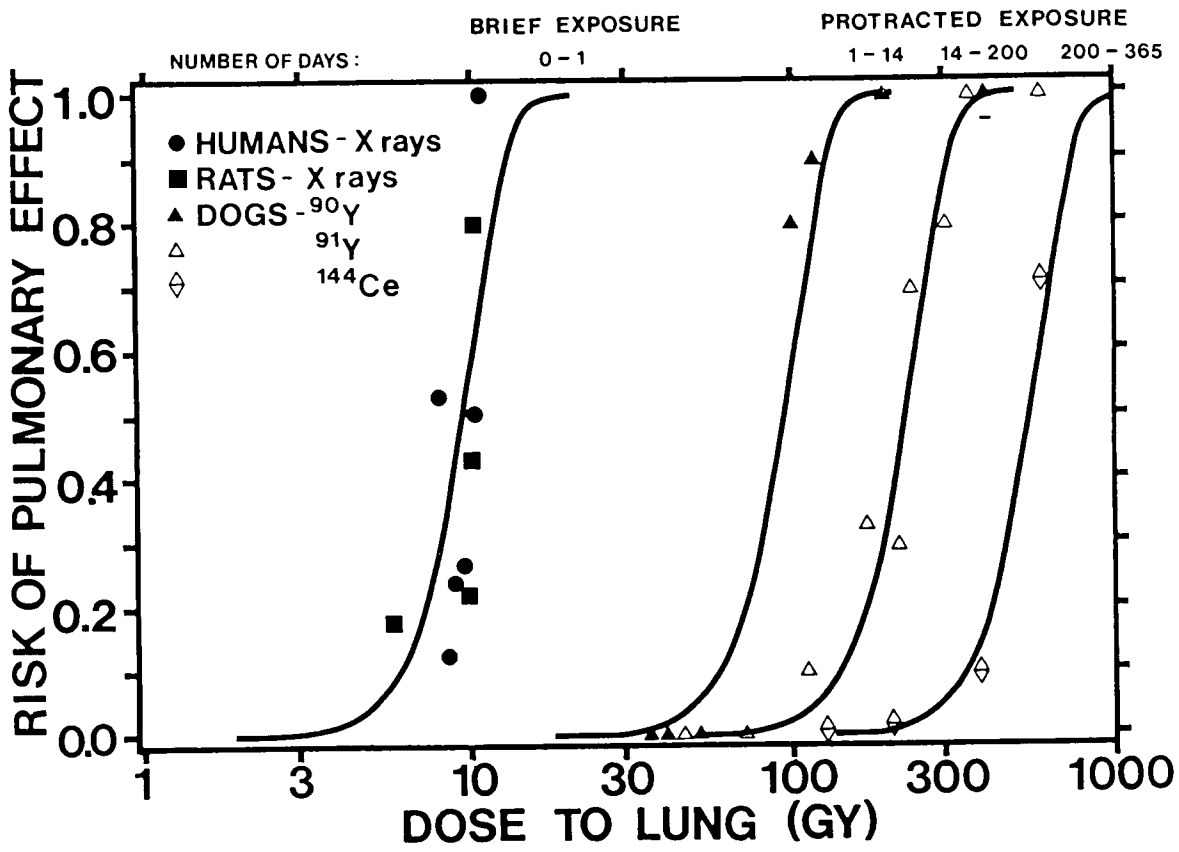

Figure 1.8 Dose-effect relationships for mortality effects of lung irradiation.

The data for pneumonitis in humans is based on a recent report by Van Dyk et al. (1981), for exposure of the thorax. Most individuals with pneumonitis died. The data for upper-body exposure of rats are from Dunjic et al. (1960). The radionuclide data are from McClellan et al. (1982), reanalyzed by others (Scott and Seiler, 1984). These curves demonstrate the effect of dose protraction in the lung.

Table 1.7 Relationship Between Average Lung Dose and Likely Survival Time for Those Individuals Receiving Lethal Injury after Exposure to Low-LET Radiation

Time in Which Dose is Delivered (days)	Estimated D_{50} (Gy)	Likely Time to Death (Days)
Within 1 day	9.5[a]	30-210[a]
Within 14 days	94[b]	10-250[b,c]
Within 200 days	220[b]	100-550[b,c]
> 200 days	540[b]	200-900[b,c]

[a] Based on earliest occurrence of radiation pneumonitis in humans (Van Dyk, et al., 1981).

[b] Based on dogs exposed via inhalation to insoluble aerosols containing the beta emitters ^{90}Y, ^{91}Y, ^{144}Ce, ^{90}Sr.

[c] Assuming rather broad distribution of initial lung deposition in case of inhalation exposure. Relatively large initial depositions would lead to survival times near the smallest value listed; relatively small but lethal levels would lead to survival times close to the largest value listed.

1.2.5.2 Dose-Effect Relationship: Mortality

Determination of a median dose that would result in early death from radiation-induced thyroid disease is not possible. The numbers of such deaths are insufficient to develop realistic risk estimates. Generally, radiation-induced early effects in the thyroid respond to medical treatment and do not result in death.

1.2.5.3 Dose-Effect Relationship: Morbidity

Sufficient information is available to develop dose-effect relationships for illness from acute radiation thyroiditis and hypothyroidism, but it is insufficient for developing a relationship for chronic lymphocytic thyroiditis. New information about morbidity from thyroid irradiation has been developed and is reviewed in Appendix A.

1.2.5.3.1 Acute Radiation Thyroiditis

The median dose for producing acute radiation thyroiditis and the shape parameter for the dose-effect curve are shown in Table 1.8 and Figure 1.9. The D_{50} of 1200 Gy for doses protracted over 1 to 21 days was estimated from studies of patients given ^{131}I for ablation of the thyroid as noted in Appendix A (see Section A.7). Above the apparent 200 Gy threshold, about 5% of the exposed individuals would be estimated to develop thyroiditis for each 100 Gy increment in dose if a linear function were used. A Weibull function, which is approximately linear, is used for systematic treatment of all early effects risk estimates. This D_{50} of 1200 Gy applies to protracted radiation doses because the effective half-life of ^{131}I in the thyroid is 6 days.

Clinically evident radiation thyroiditis after acute or fractionated external radiation therapy or accidental exposure has not been reported. Thus, a D_{50} for brief irradiation cannot be determined directly. It is also unlikely that an individual would receive an accidental external dose sufficient to cause acute thyroiditis without receiving lethal injury to the bone marrow.

1.2.5.3.2 Hypothyroidism

The median effective dose for producing hypothyroidism and the shape parameter for the response curve are given in Table 1.9. The dose-effect relationship shown in Figure 1.10 is in agreement with a linear relationship for low levels of risk. The primary D_{50} of 300 Gy for protracted doses from ^{131}I was estimated from an analysis of studies of Graves' disease (hyperthyroidism) patients treated with ^{131}I (Maxon *et al.*, 1977) as noted in Appendix A (see Section A.9 and Table A.8). Estimates of dose for ^{131}I include both beta and gamma irradiation and depend to some extent on the distribution of ^{131}I in the gland.

A D_{50} of 60 Gy for brief (0 to 1 day) irradiation was derived from the D_{50} for ^{131}I using a dose-effect modifying factor for protracted ^{131}I beta-irradiation to brief x-irradiation of 1/5 (see Appendix A, Section A.9.3). The D_{50} of 60 Gy is consistent with the results from a recent study of external x-irradiation of the thyroid (Kaplan *et al.*, 1983) in which biochemical hypothyroidism was found in 42 of 95 patients evaluated 19 years after an average thyroidal dose of 30 Gy. The threshold doses are estimates based on clinical impressions gained from external irradiation of the thyroids in children (Maxon *et al.* 1980). It is noteworthy that the

Table 1.8 Median Dose Estimates (D_{50}) and Response Curve Shapes (V) for Acute Radiation Thyroiditis After Thyroid Irradiation[a]

Parameter[b]	Time Period of Dose Accumulation
	1-21 Days
D_{50} (Gy)	1,200
Slope (V)[c]	1.9
Threshold (Gy)	200

[a]Based on information in Appendix A, Section A.7. No estimates are made for brief periods since no clinically evident cases of radiation thyroiditis are reported after acute or fractionated external irradiation and it is unlikely that sufficiently high external doses could be delivered to the thyroid in an accident without causing mortality.

[b]Parameters based on ^{131}I deposition in thyroid.

[c]Slope = $2.6/\ln (D_{50}/D_5)$.

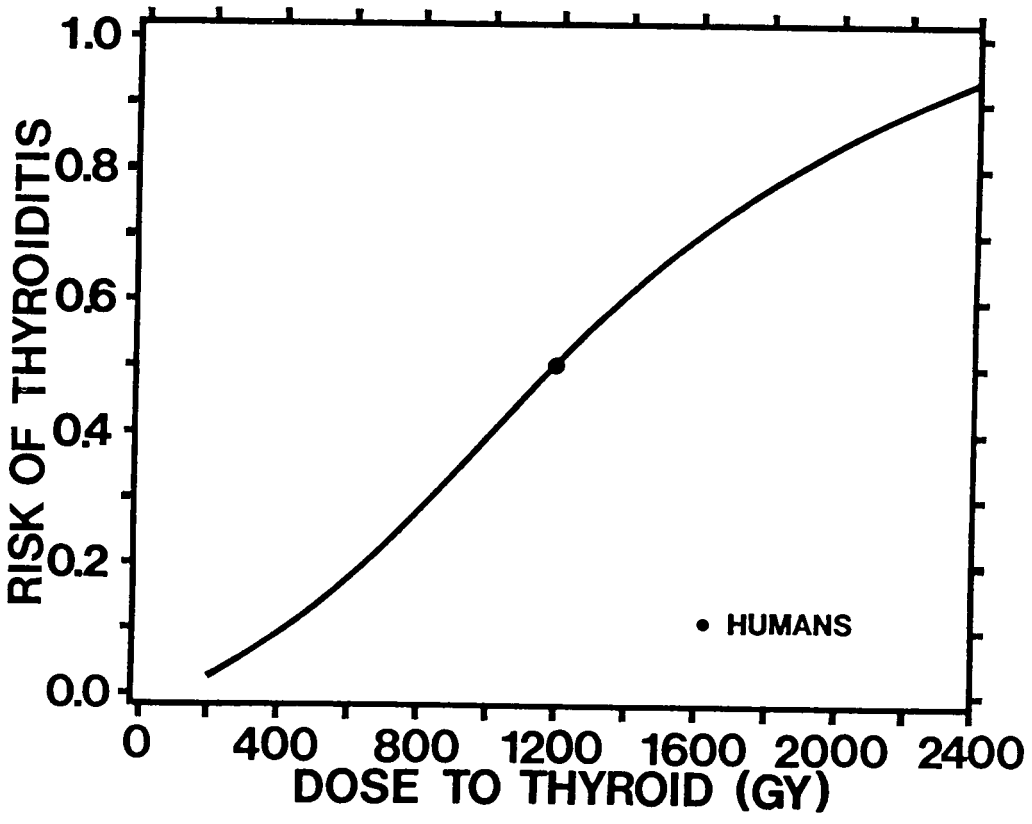

Figure 1.9 Dose-effect relationship for radiation thyroiditis. Based on data for patients treated with ^{131}I (See Table 1.8).

Table 1.9 Median Dose Estimates (D_{50}) and Response Curve Shapes (V) for Hypothyroidism After Thyroid Irradiation

Parameter	Time Period of Dose Accumulation	
	0-1 days[a]	1-21 days[b]
D_{50} (Gy)	60[c]	300[d]
Slope (V)[e]	1.3	1.3
Threshold (Gy)	2[c]	10[d]

[a]Based on external low-LET irradiation.

[b]Based on ^{131}I deposition in thyroid.

[c]Based on Table A.8 in Appendix A. Threshold estimate is 2 Gy and 100% incidence in 5 years is about 120 Gy for external x or gamma irradiation.

[d]Based on Table A.8 in Appendix A. Threshold estimate is about 10 Gy and 100% incidence is about 600 Gy for ^{131}I incorporated in the thyroid.

[e]Slope - $2.6/\ln (D_{50}/D_5)$.

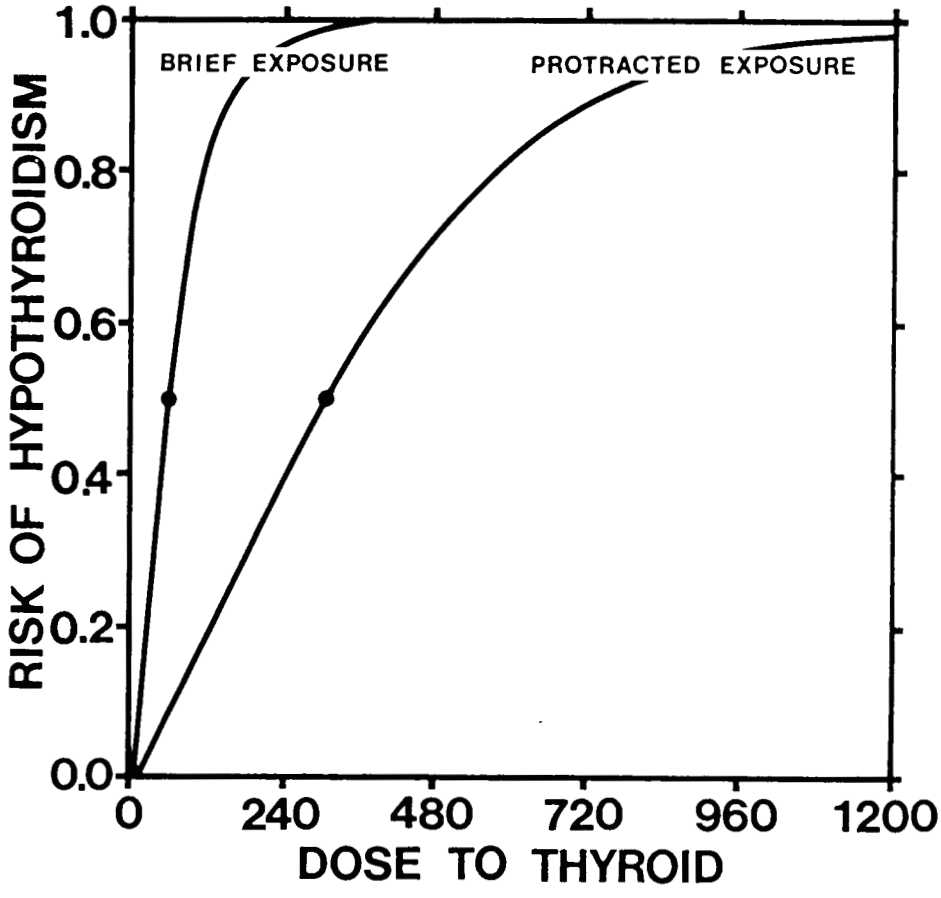

Figure 1.10 Dose-effect relationships for hypothyroidism after exposure to external low-LET irradiation or ^{131}I.

Based on data from Table 1.9. Brief exposure represents exposure from 0-1 day external low-LET irradiation. Protracted exposure represents 1-21 days ^{131}I internal exposure.

Marshallese exposed to nuclear weapons testing fallout have a definite increased incidence of hypothyroidism, as indicated by increased serum TSH concentrations (see Appendix A, Section A.9.3). Doses of about 7.9 Gy were delivered to their thyroids from external irradiation and internally deposited radioiodines.

1.2.6 Skin

1.2.6.1 Early Radiation Effects

Early radiation effects in the skin can be classified as: (1) erythema, (2) transepidermal injury, and (3) dermal necrosis (NCRP Report 42, 1974).

Erythema is a reddening of the skin equivalent to a first degree thermal burn or sunburn. After a single, large exposure, erythema may appear within minutes to hours. With lower doses, redness may not appear for several weeks. Dry desquamation, or scaling, usually follows the erythema, but medical care is not necessary.

Transepithelial injury or moist desquamation is equivalent to a second degree thermal burn in which blisters form in the epidermis. Soon after exposure, erythema occurs, followed by blister formation in 1 to 2 weeks, depending on the magnitude of the dose. Medical care is often needed for these types of injuries, which usually heal with proper attention. The new skin, however, is usually pigmented, thin, and easily injured.

Dermal necrosis is a severe injury in which there is widespread cell destruction in the skin and underlying tissues and sloughing of the epidermis. The lesions resemble those caused by severe scalding or chemical burns with accompanying intense pain. Medical treatment is required and may involve skin grafting or amputation of the affected limb.

Many factors influence the skin response to ionizing radiation (Langham 1487, p. 64, 1967). The severity, time of appearance, and duration of the skin response as a function of radiation dose may depend on such variables as: 1) time over which the radiation occurs, 2) dose rate, 3) depth-dose distribution, 4) quality (LET) of the radiation, 5) area of skin irradiated, 6) anatomical region irradiated, and 7) presence of other irritants or trauma.

The depth-dose distribution is particularly important in beta-irradiation (Moritz and Henriques, 1952). Studies on pig skin (which is often studied because of its similarity to human skin) show that a depth of about 0.09 mm is critical for the induction of transepithelial injury (Table 1.10). This depth corresponds roughly to the location of the basal cells of the epidermis. These are regenerative cells, and injury to them is likely to be the biologic basis for identifying this critical depth. Only the radiation dose to a depth greater than 0.09 mm should be considered capable of inducing a full radiation reaction in skin.

More recent studies of the skin of mice and pigs exposed to beta emitters have emphasized the importance of beta energy and area irradiated in determining the severity of effects (Coggle *et al.,* 1984; Peel and Hopewell, 1984). The doses required to produce transepithelial injury in 50% of exposed pigs to 15 to 22.5 mm diameter fields were 30-45 Gy for ^{90}Sr, 80 Gy for ^{147}Tm, and 500 Gy for ^{147}Pm. It was hypothesized that repair of the skin injured with high energy beta irradiation proceeded from the periphery of the irradiated field and that the repair for low energy beta irradiation occurred from hair follicle epithelium deep in the dermis. An area effect was observed in the epithelial response to ^{90}Sr irradiation.

Table 1.10 Dose of Transepidermal Beta Radiation Required for Production of Transepithelial Injury in the Skin of Pigs[a]

Radionuclide	Average Energy (MeV)	Surface Dose Required to Produce Injury (Gy)	Depth Dose (0.09mm) Required to Produce Injury (Gy)
Sulfur-35	0.17	200	12
Cobalt-60	0.31	40	16
Cesium-137	0.55	20	17
Yttrium-91	1.53	15	12
Strontium-90/ Yttrium-90	0.61 2.20	15	14
			Average 15

[a]Moritz and Henriques, 1952

The effective dose 50% for transepithelial injury ranged from ~25 Gy for a 40 mm diameter irradiation field to ~450 Gy for a 1 mm diameter field.

1.2.6.2 Dose-Effect Relationship: Mortality

No dose response relationships were calculated for death from radiation skin burns. Although such deaths might theoretically be possible if very large areas of the body were burned, it is highly unlikely that this would be a practical problem. The likelihood of the protection of normal street clothing and early removal of deposited beta emitters and the unlikelihood of accident scenarios resulting in radionuclides being released that cause large skin burns without causing other more serous problems are points against mortality from skin burns being a practical problem.

1.2.6.3 Dose-Effect Relationship: Morbidity

Dose-effect relationships for radiation injury to skin were not developed in the Reactor Safety Study (WASH 1400, 1975). However, a few systematic clinical investigations have been performed that can form a basis for deriving limited dose-effect relationships for erythema and transepithelial injury. No information on dermal necrosis is available on which to develop dose-effect relationships. A vast literature describing reactions of normal and diseased human skin is available, but it relates mainly to the special needs and dose schedules of clinical radiotherapy. The risk estimates derived in this section are compatible with general clinical experience. However, the dose estimates are provisional and uncertain (Langham, 1967). The D_{10} doses used to determine the shape of the dose-response curve may be in error $\pm$ 50%, but errors in the D_{50} estimates should be less.

Risk functions that depend on the area of the skin irradiated were not developed. Those presented are applicable for exposed areas of 35 to 100 cm^2. Smaller irradiated fields lead to an increase in the D_{50} estimates (Peel and Hopewell, 1984; Coggle *et al.*, 1984).

1.2.6.3.1 Erythema

The median dose for skin erythema and the shape of the dose-effect curve are noted in Table 1.11 and Figure 1.11. The D_{50} of 6 Gy for brief irradiation is based on studies of Duffy *et al.* (1934) as analyzed by the Space Radiation Study Panel (Langham, 1967). The data are for 200 kVp filtered x-rays administered at a rate of 60 R/min. The radiation doses ranged from 5 Gy to 7.5 Gy. The doses were estimated for a 0.1-mm depth in the skin and on an area exposed of 35 to 100 cm^2. The D_{50} of 10 Gy for protracted irradiation (1 to 14 days) is derived by multiplying D_{50} for brief irradiation by a protraction factor of 1.7 (Langham, 1967). Protraction of skin irradiation into equal daily dose fractions has a sparing effect that can be demonstrated with a logarithmic isoeffect plot with a slope of 0.22 to 0.33.

1.2.6.3.2 Transepithelial Injury

The median dose for transepithelial injury and the shape of the effect curve are noted in Table 1.11 and Figure 1.11. The D_{50} of 20 Gy for brief irradiation is based on analysis of clinical radiation therapy experience (Langham, 1967) and with exposure conditions similar to those used for erythema. This estimate is consistent with the value of approximately 25 Gy based on ^{90}Sr irradiation of 40 mm diameter areas of pig skin (Peel and Hopewell, 1984).

Table 1.11 Median Dose Estimates (D_{50}) and Response Curve Slopes (V) for Skin Erythema of Transepithelial Injury After External Irradiation

Effect	Parameter	Time Period of Dose Accumulation[b]	
		0-1 days	1-10 days
Erythema	D_{50} (Gy)[a]	6[c]	10[d]
	Slope V	5.2[e]	5.2
Transepithelial Injury	D_{50} (Gy)	20[c]	[34[d]]
	Slope V	5.3[e]	[5.3]

[a]Based on data of Duffy et al., as analysed by the Space Radiation Study Panel NAS/NRC #1487, p. 63, 1967.

[b]Dose estimation at 0.1 mm depth in skin; area exposed, 35 to 100 cm^2; low-LET radiation.

[c]Based on 200 KVP x-rays 60 R/min.

[d]Derived by multiplying the D_{50} for brief exposure by a protraction factor of 1.7 (NAS/NRC #1487, p. 65, 1967).

[e]Slope V = $1.9/\ln(D_{50}/D_{10})$.

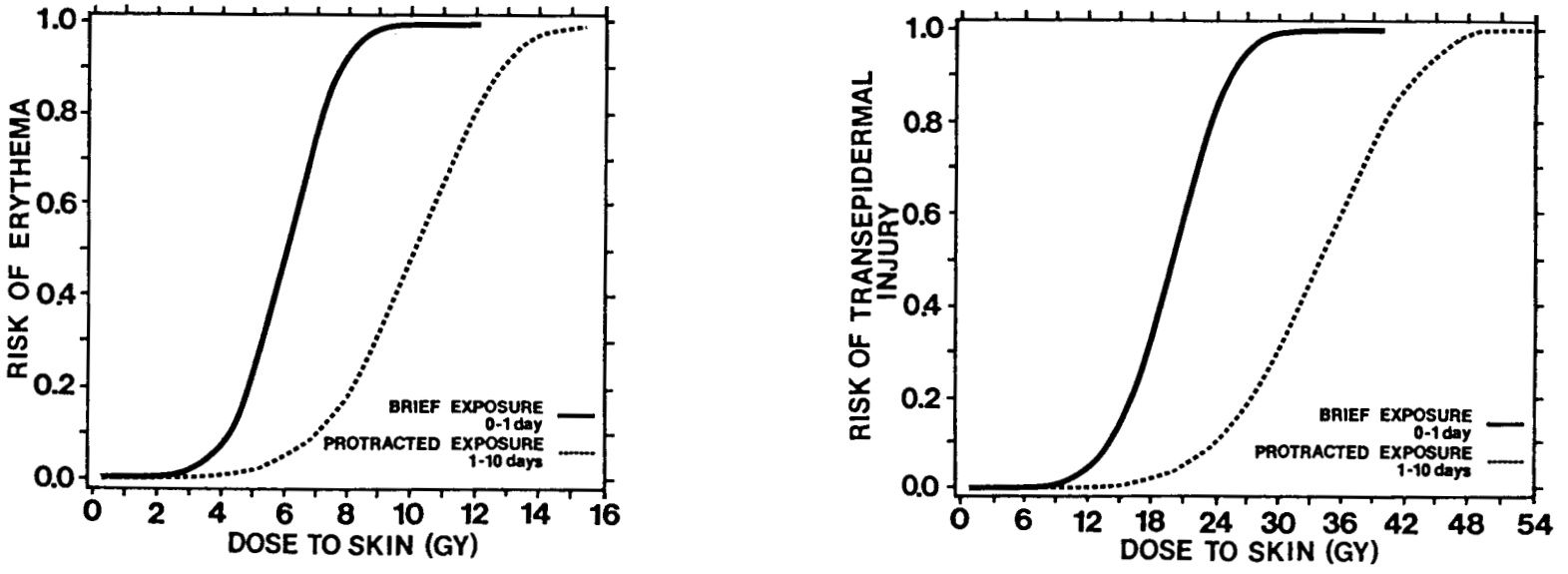

Figure 1.11 Dose-effect relationship for skin erythema.

Based on studies of Duffy et al. as analyzed by the Space Radiation Study Panel (Langham, 1967). Also shown is a dose-effect relationship for transepithelial injury based on clinical data (Langham, 1967).

The D_{50} of 34 Gy for protracted irradiation is derived by multiplying the D_{50} for brief irradiation by a protraction factor of 1.7, which is assumed to be the same as that used in projecting the erythema dose-effect relationships.

1.2.7 Gonads

1.2.7.1 Early Radiation Effects on the Ovaries

The ovary, a relatively radiosensitive organ, contains a fixed number of germ cells that cannot be replaced if severely damaged by radiation. A loss of all ova leads to permanent sterility. Doses causing temporary sterility in females range from 1.5 to 2 Gy for brief exposure to low-LET external irradiation (UNSCEAR, 1982). Temporary sterility in women has been caused by doses ranging from 1.7 to 6.4 Gy for brief single exposure. Higher doses are required when the dose is delivered in fractions. Doses of 3.2 to 10 Gy cause permanent sterility. It has been estimated that a dose of 6 Gy will ablate the human primordial oocyte population.

The radiosensitivity of the ovary depends on age at exposure, although the age dependence is difficult to resolve.

On the basis of radiation therapy data (WASH 1400, 1975; Lushbaugh and Ricks, 1972; Rubin and Casarett 1968), doses of about 1.25 to 1.5 Gy to the ovaries may produce prolonged or permanent suppression of menstruation in about 50% of women, and 6 Gy is thought to be sufficient for permanent suppression. Protraction of the dose over 2 to 6 weeks would cause the dose required for these effects to increase (WASH 1400, 1975).

Peck *et al.* (1940) carefully documented data for permanent sterility based on 334 patients exposed to photon radiation. Women 40 or more years of age were more sensitive than those under 40. These data were used to develop a dose-effect relationship for permanent sterility as shown in Figure 1.12. Parameters for the dose-effect relationship are for brief exposure during the first day following an accident. Available information (Ray *et al.,* 1970; Thomas *et al.,* 1976) was also used to develop a dose-effect relationship for protracted exposure. Results are summarized in Table 1.12.

1.2.7.2 Early Radiation Effects on the Testes

The testes are also quite sensitive to radiation (UNSCEAR, 1982). Doses as small as 0.1 Gy have caused temporary sterility. Doses of 2 to about 6 Gy or more are required for permanent sterility. The dose required to reduce the Type B spermatogonia to 37% of the initial number has been estimated to be only about 0.2 Gy. Recovery time in men is dose-dependent and may require many years after exposure to large doses.

Japanese fishermen exposed to weapons testing fallout received 1.4 to 6 Gy of gamma rays over 14 days. Their sperm counts were severely depressed; however, recovery began by 2 years and most men subsequently fathered healthy children (Freedman and Keehen, 1966; UNSCEAR, 1982).

The testes is unusual in that fractionated exposure may lead to more damage than the same dose delivered in a single exposure. It was observed that 20 exposures to 0.25 Gy each caused a more rapid depletion and slower recovery than did a single dose of 5 Gy (Lushbaugh and Ricks, 1972; UNSCEAR, 1982).

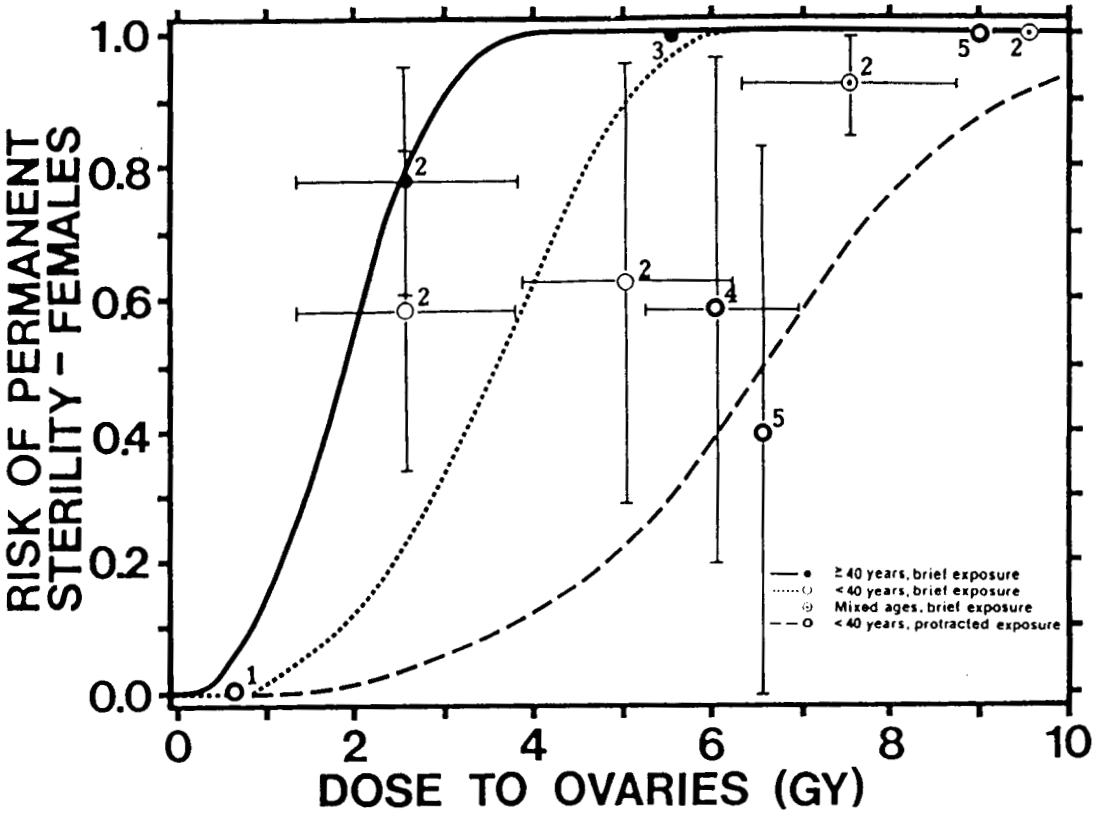

Figure 1.12 Dose-effect relationship for permanent sterility in females. Origin of the data:

(1) 700 women treated for sterility, 0.6 Gy over 2 weeks in fractions;

(2) (Peck et al. 1940; Rubin and Casarette, 1968) Single doses with two age groups (< 40 years, > 40 years);

(3) Fractionated exposure (Doll and Smith, 1968; Smith and Doll, 1976; Ash, 1984), ages > 40 years;

(4) 7 women 13-32 years of age received fractionated exposure (Ray et al., 1970; cited from Ash, 1980);

(5) 12 of 22 woman treated for Hodgkins disease with Oophoropexy and fractionated exposure at 6.5 Gy total dose (Thomas et al., 1976).

Table 1.12 Median Dose Estimates (D_{50}) and Response Curve Slope (V) for Temporary Sterility in Males and Permanent Sterility in Females

Sex	Age	Exposure Period	Effect	D_{50} (Gy)	V
Female	≥40	Brief[a]	Permanent Sterility	1.9[c]	3[d]
Female	<40	Brief	Permanent Sterility	2.6[c]	3[d]
Female	≥40	Protracted[b]	Permanent Sterility	[4.6][i]	3[d]
Female	<40	Protracted	Permanent Sterility	6.3[e]	3[d]
Male	All	Brief	Temporary Sterility	0.7[f]	10[g]
Male	All	Protracted	Temporary Sterility	0.4[h]	10[g]

[a]Dose delivered in 0-1 days to ovaries or testes.

[b]Dose delivered after 1 day to ovaries or testes.

[c]Based on data from Peck et al. (1940) cited from WASH 1400 (1975).

[d]Also based on data of Peck et al. assuming V independent of age and dose rate.

[e]Based on data from Ray et al. (1970) and Thomas et al. (1976).

[f]Based on data of Thorsland and Paulson (1972) and Rowley et al. (1974, 1975).

[g]Based on data of Thorsland and Paulson (1972), Rowley et al. (1974, 1975), Sandermann(1966) and Hahn et al. (1982). Assumes V is independent of dose rate.

[h]Based on data of Sandermann (1966) and Hahn et al. (1982).

[i]Based on protraction factor of 6.3/2.6=2.42 derived from numbers in this table.

Parameters of the dose-effect curve for sterility in males are given in Table 1.12. Dose-effect relationships are given in Figure 1.13 for both brief and protracted exposure.

1.2.8 Fetus

1.2.8.1 Early Radiation Effects

The classic effects of radiation on the developing mammalian embryo or fetus are embryonic death, gross congenital malformations, and intrauterine growth retardation (UNSCEAR, 1977; Hoffman *et al.*, 1981; Brent, 1980). In laboratory animals, the greatest sensitivity to the lethal effects of radiation is during early pregnancy, before the embryo is implanted. There is no confirming evidence in women that this radiosensitive preimplantation stage is present in humans. This may be due to an early unnoticed loss of the zygote. Although there are a number of studies in laboratory animals to confirm this, it has been argued that the disparity in the timing of intrauterine development between women and laboratory animals makes the intraspecies extrapolation of data invalid (Mole, 1982).

The cardinal congenital malformations of intrauterine radiation in humans are the central nervous system effects, microcephaly (i.e., small head circumference), and eye malformation (Brent, 1980). The greatest sensitivity to these malformation effects of radiation is in the early organogenesis stage. In women this time period may be well defined. New observations on Japanese atomic bomb survivors suggest that 8-15 weeks of pregnancy is the period of greatest sensitivity leading to severe mental retardation (Otake and Schull, 1984). This period coincides with the production of neurons in the cerebral hemispheres in the human species and with concepts of enhanced radiosensitivity in dividing cell populations. No significant risk could be demonstrated for 0-8 weeks postconception. For greater than 15 weeks the risk was less than for the 8-15-week period (Otake and Schull, 1984). Studies of humans exposed randomly during pregnancy to high doses of radiation indicate that microcephaly is the most common malformation (Miller and Mulvihill, 1976). An additional important finding was that no visceral, limb or other malformations were found unless the child exhibited microcephaly, readily apparent eye malformations or intrauterine growth retardation.

1.2.8.2 Dose-Effect Relationship

There is evidence in data on the Japanese A-bomb survivors that doses below 0.5 Gy may have caused mental and growth retardation. A dose-effect curve for small head circumference, based on individuals exposed between 0 and 17 weeks of gestation (Miller and Blot, 1972; WASH 1400, 1975) is given in Figure 1.14. Parameters associated with the dose-effect relationship are shown in Table 1.13. Some information is available on the influence of dose rate on fetal malformation and suggests that lowering the dose rate or fractionating the dose leads to a sparing effect (UNSCEAR, 1977). These dose-effect relationships may be changed pending the reevaluation of the mental retardation data on the Japanese bomb survivors and the radiation dose estimates at the bomb sites.

In the recent study of Otake and Schull (1984), the prevalence of mental retardation among children irradiated *in utero* during the bombing of Hiroshima and Nagasaki was reported. A child was considered mentally retarded if he or she was unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized. Most of these children were never

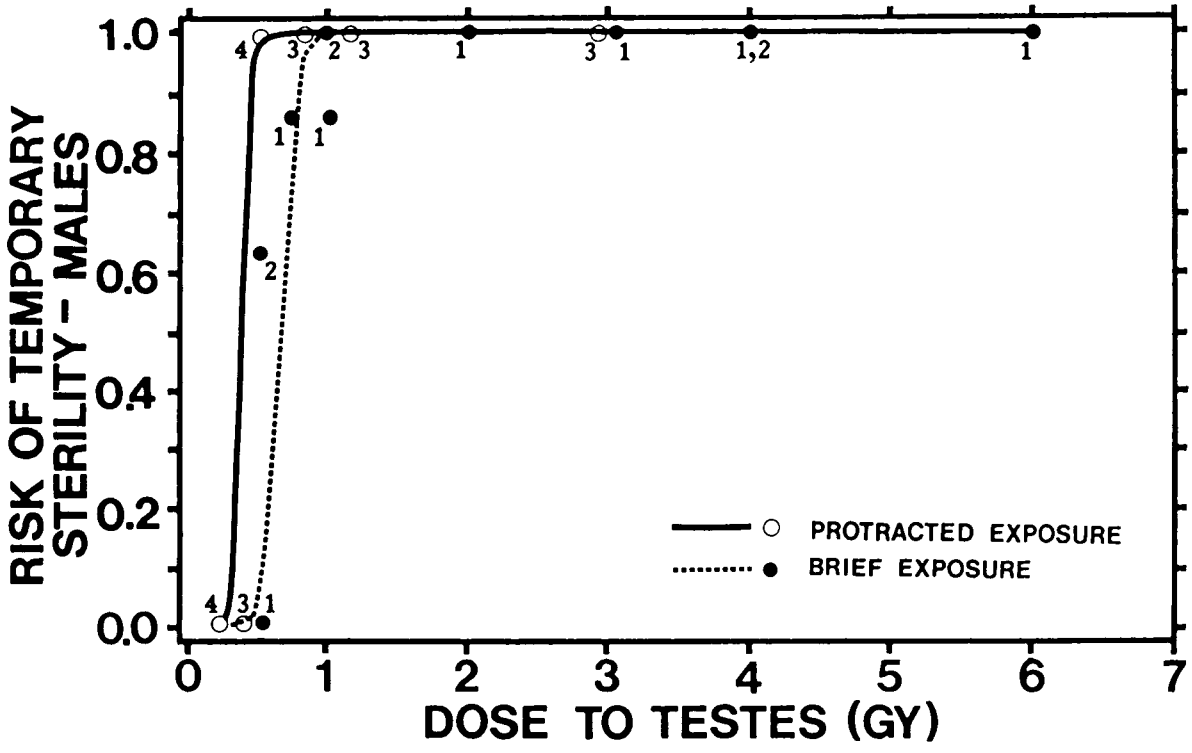

Figure 1.13 Dose-effect relationahip for temporary sterility in males after exposure to low-LET radiation. Source of data:

(1) 67 healthy humans (volunteers) receiving testicular irradiation (Rowley et al., 1974, 1975), in a brief exposure;

(2) 64 volunteers receiving brief testicular irradiation;

(3) 26 patients treated for seminoma via fractionated exposure (Hahn et al., 1982);

(4) 44 males with one testis removed because of a testicular tumor treated by fractionated exposure (Sandermann, 1966; Ash, 1980).

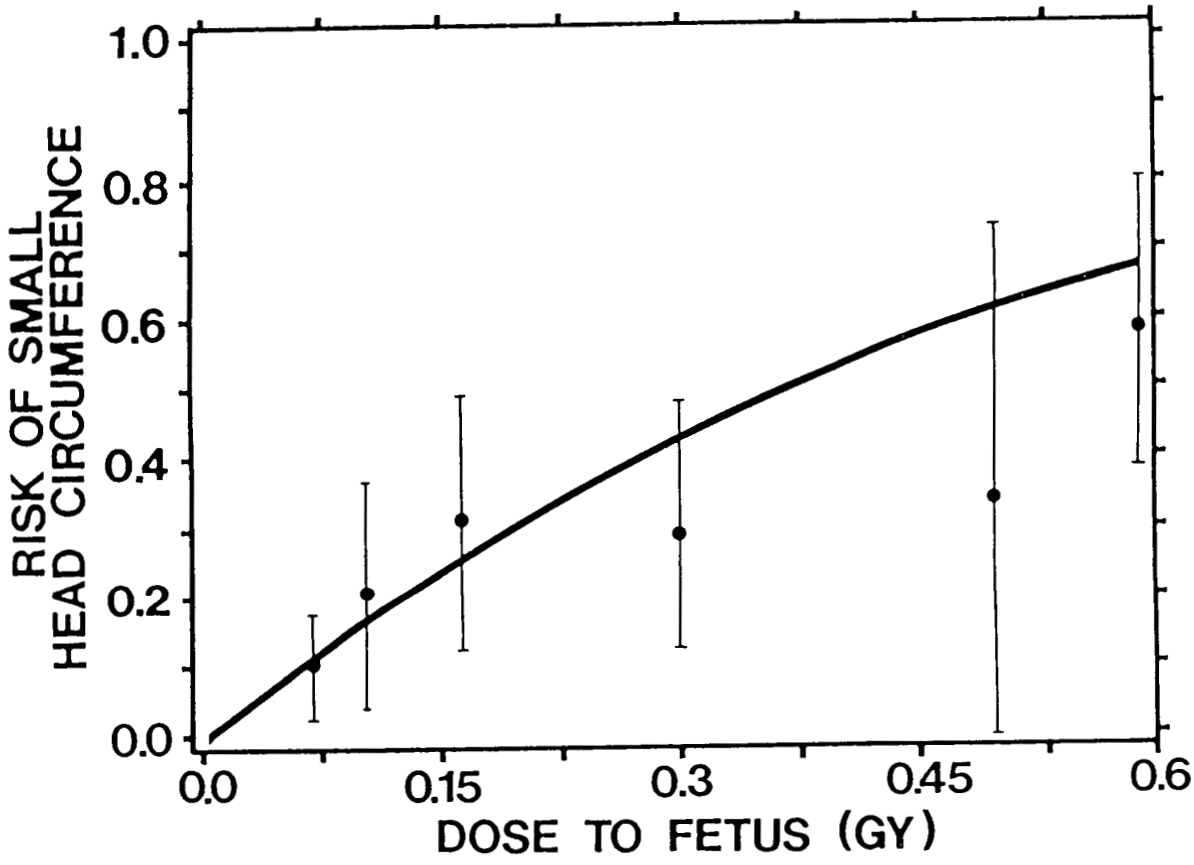

Figure 1.14 Dose-effect relationship for reduced head circumference.

Based on individuals exposed between 0 and 17 weeks of gestation in Hiroshima (Miller and Blot, 1972). The dose, D_{50}, in Gy represents the dose to the fetus obtained using an organ dose to kerma ratio of 0.39 (BEIR III, 1980; Kerr,1979). Error bars represent plus or minus two standard errors based on a binomial distribution.

Table 1.13 Median Dose Estimate (D_{50}) and Response Curve Slope (V) for Small Head Size After in utero Exposure During First Day Following Accident[a]

Parameter	Value
D_{50} (Gy)	0.37
Slope V	1.0

[a]Based on data from Miller and Blot (1972; WASH 1400, 1975).

Individuals exposed between 0 and 17 weeks of gestation in Hiroshima. The D_{50} in Gy is the dose to the fetus obtained using an organ-dose-to-kerma ratio of 0.39.

enrolled in a public school; the few that were all had IQ values less than 70. The highest prevalence of mental retardation occurred at the 8-15 weeks gestational age. This is the time period when the most rapid proliferation of neuronal elements occurs and when most, if not all, neuroblast migration to the cerebral cortex from the proliferative zones occurs (Otake and Schull, 1984). Dose-effect relationships based on the data are given in Figure 1.15. The fitted curves are based on the assumption of a linear cumulative hazard function and represent estimates of the excess risk. Model parameters D_{50} and V are given in Table 1.14.

Evidence for prenatal and neonatal death in humans caused by irradiation of the pregnant mother and conceptus is limited. Because of the lack of quantitative data on effects of irradiation of humans, results of animal experimentation have been extrapolated to humans (Brent and Gorson, 1972). Results are summarized in Figure 1.16 and Table 1.15.

1.2.9 Eyes

Different components of the eye have different radiosensitivities. The lens is especially sensitive when uniformly irradiated (UNSCEAR, 1982). Epithelial tissues around the eye seem to have a radiosensitivity similar to that of skin. In humans, cataracts are caused by brief single 2-Gy doses of low-LET radiation; about 4 Gy are required when the dose is fractionated. There is a dose-effect relationship. The latent period varies from about 0.5 to about 35 years with an average of about 2 to 3 years (UNSCEAR, 1982). Minimum stationary opacities have been associated with single doses of 1 to 2 Gy. A dose of 5 or more Gy causes serious progressive cataracts. The incidence of cataract formation at 7.5 Gy (single-dose exposure) is 100%. Protraction or fractionation of the dose leads to a sparing effect. A dose of 10 Gy delivered over 3-12 weeks caused cataracts in 75% of those exposed, and 14 Gy led to 100% incidence. Recent results suggest that the threshold for cataract formation after fractionated or protracted exposure is in the 6- to 14-Gy range (Charles *et al.*, 1978; Bendael *et al.*, 1978).

Dose-effect information based on these findings is summarized in Tables 1.16 and 1.17. Dose-effect relationships are plotted in Figure 1.17.

1.3 Models for Combining Risks

Hazard-function modeling techniques can be used to predict the combined single-organ effects of brief and protracted low-LET radiation, and to predict the combined effects of multiple organ injuries. Only effects that can be considered quantal, such as mortality, are discussed. Morbidity can also be considered quantal if the level of severity is not considered. Such quantal effects can be described by using one of several functions that are related. These include the risk function R, the survival function S, and the cumulative hazard function H.

Risk functions are often used in the calculation of the expected cases of cancer and genetic disorders. This was done in the BEIR III report (1980) and is done in Volume II, Chapters 2 and 3 of our report. Survival functions are often used in the investigation of cell killing effects of radiation. The cumulative hazard is less known but provides a useful way to model single or combined effects of different toxicants.

Examples of some recent applications of hazard-function modeling techniques are given in Table 1.18. The risk, survival, and cumulative hazard are related by the expression

$$R = 1 - S = 1 - e^{-H} \tag{1.7}$$

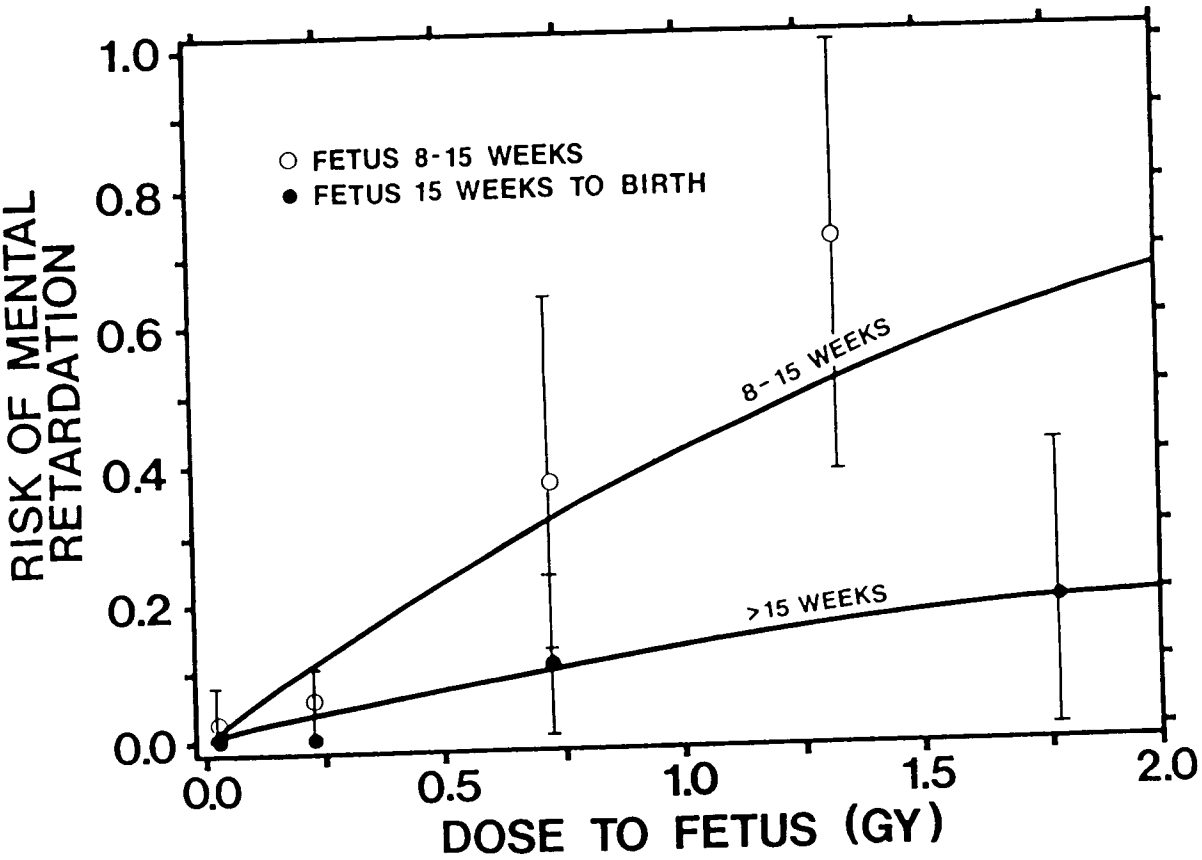

Figure 1.15 Dose-effect relationships for mental retardation.

Based on children irradiated in utero by A-bomb detonation analysed by Otake and Schull (1984). Two gestational age ranges are provided: 8-15 weeks and greater than 15 weeks. For less than 8 weeks the risk is assumed to be negligible. Error bars represent plus of minus two standard errors which are based on a binomial distribution.

Table 1.14 Estimates of the D_{50} and Shape Parameter for Weibull Risk Estimator for Mental Retardation Following In Utero Exposure[a]

Gestational Age (Weeks)	D_{50} (Gy)	V
0 - 7	-	-
8 - 15	1.3	1
> 15	5.6	1

[a]Based on data from Otake and Schull (1984). D_{50} in Gy is dose to fetus.

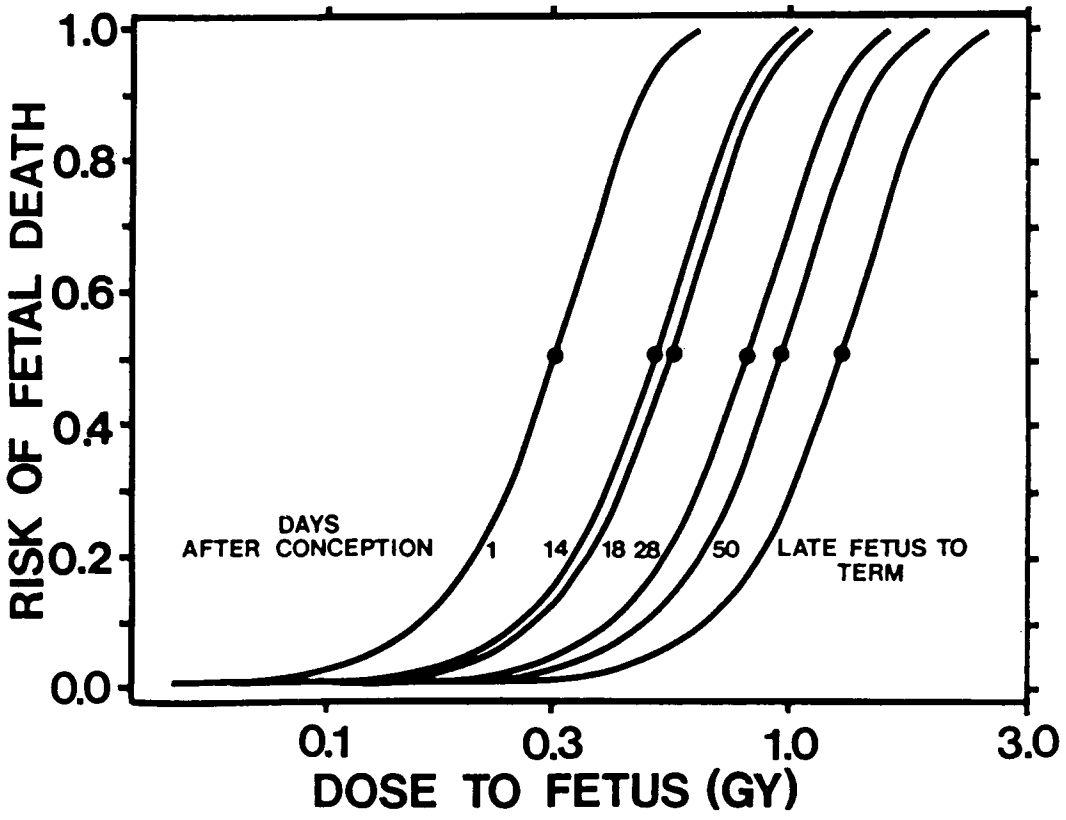

Figure 1.16 Dose-effect relationships for prenatal and neonatal death in humans caused by exposure of the conceptus.

Based on same information as was used in the Reactor Safety Study (WASH 1400, 1975).

Table 1.15 Median Dose Estimates (D_{50}) and Response Curve and Slopes, (V) for Lethality Risks for the Human Fetus[a,b]

Time After Conception	Median Dose (D_{50}) (Gy)		Slope[c] (V)
	Maternal	Fetal	
Day 1	0.67-0.95	0.26-0.37	1.98
Day 14	1.33	0.52	2.5
Day 18	1.43	0.56	3.8
Day 28	2.09	0.82	-
Day 50	2.47	0.96	-
Late Fetus to Term	2.85-3.8	1.1 -1.5	-

[a]Based on data from Brent and Gorson (1972); WASH 1400, (1975); Conversions from R to Gy based on factor of 0.0095 Gy/R.

[b]Organ dose to kerma ratio of 0.39 used (BEIR III, 1980; Kerr, 1979)

[c]Reported minimal lethal doses were used as an estimate of the dose associated with a 1% incidence of deaths to estimate the slope parameter V.

Table 1.16 Risk Estimates for Injury to the Ocular Lens (Cataracts) from Brief Low-LET Irradiation[a]

Dose (Gy)	Risk
2.4[b]	0.1
3.1[c]	0.5
3.9[d]	0.9

[a](NAS/NRC 1487,p.138, 1974); Values should be regarded as uncertain.

[b]Estimated dose for a 10% incidence in humans.

[c]Estimated dose for a 50% incidence in humans.

[d]Estimated dose for a 90% incidence in humans.

Table 1.17 Median Dose Estimate (D_{50}) and Response Curve Slope (V) for Injury to the Ocular Lens (Cataracts)

Parameter	Time Period of Dose Accumulation		
	0-1 day	1-14 days	> 14 days
D_{50} (Gy)	3.1	6.2[a]	9.3[b]
Slope (V)[c]	7.4	7.4	7.4

[a]Based on dose rate protraction factor of 2. (NAS/NRC 1487, p.139, 1974)

[b]Based on dose rate protraction factor of 3. (NAS/NRC 1487, p.139, 1974)

[c]Assumed to be independent of dose rate.

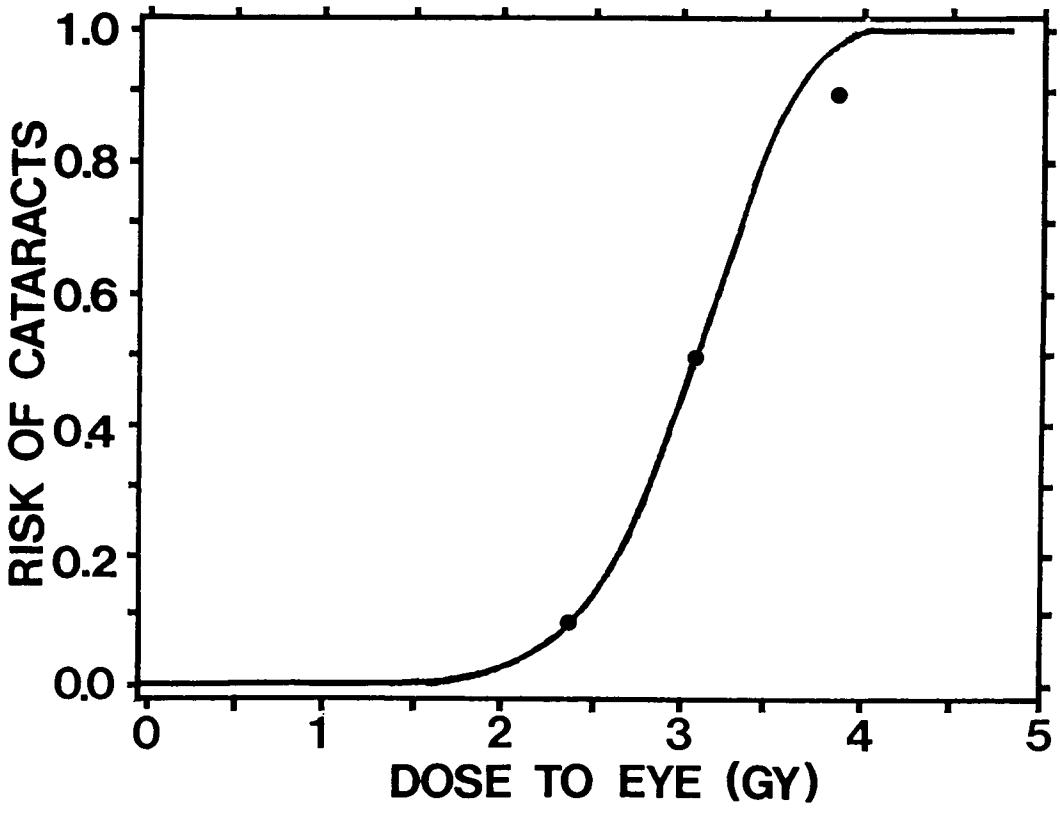

Figure 1.17 Dose-effect relationship for injury to the eyes (cataracts) applicable for brief exposure during the first day following an accident.

Based on data from NAS/NRC 1487, p. 138, 1974.

Table 1.18 Applications of Hazard Function Modeling Techniques

Application	Reference
Cell Killing by Combined Exposure to different radiations	Zaider and Rossi, 1980; Scott, 1983, 1984
Cell Killing by Combined Exposure to Radiation and Chemicals	Scott, 1983
Cancer Mortality in A-Bomb Survivors. Also Relative Risk	Prentice, 1982, 1984
Lung Cancer Relative Risk For Uranium Miners Exposed to Radiation and Cigarette Smoke	Whittemore and McMillan, 1983
Cancer in Workers Exposed to Asbestos and Cigarette Smoke	McLarty and Fortson, 1983
Leukemia in A-Bomb Survivors	Brodsky et al. (in press)

If either S or H is known, then R can be found using this relationship. In the procedure to be described, an H is determined for each critical organ, in the case of mortality. These Hs are then summed to give the total hazard for lethality for the case of multiple injuries. Sufficient information is not available for effects of both brief and protracted exposure to arrive at a central risk estimates for all morbidities.

1.3.1 Single Organ and Multiple Organ Injuries

A hazard-function modeling technique has been used to derive risk estimates for mortality that could be caused by radiation exposure during a nuclear power plant accident. For each critical organ, at least two cumulative hazards are used: one for brief exposure during the first day and at least one more for the period over which the protracted internal dose is calculated. For injury to the bone marrow, three cumulative hazard functions are used: one for brief exposure during the first day, a second one for protracted exposure between 1 and 14 days, and a third one for protracted exposure between 14 and 30 days. The cumulative hazard developed for exposure during the first day is used to calculate an increment in the total hazard caused by the dose buildup during the first day. Similarly, the cumulative hazard for 1-14 days is used to calculate the increment in the total hazard caused by the dose buildup in this period. The cumulative hazard developed for a 14-30-day period is used to calculate an increment in the total hazard. Each of these increments is summed to give a total hazard associated with irradiation of the bone marrow.

A similar procedure is used for the gastrointestinal tract and for the lung. The hazard functions for these three organs are then summed to arrive at an overall hazard function for mortality from multiple organ injuries. The theoretical basis for this approach is described in detail in two recent publications (Scott, 1983, 1984). The mathematical functions used to describe the cumulative hazards were

$$H_j = ln(2) * (D_j/D_{50,j})^V \tag{1.8}$$

where j is used to indicate the period for which the function is used. For example, for bone marrow, H_1 represents the function used for brief exposure during the first day; D_1 is the dose that accumulated during the first day; and $D_{50,1}$ is the median lethal dose for brief exposure. The subscript j is equal to 2 for the 1-14-day period, and is equal to 3 for the 14-30-day period. The shape parameter V is positive and determines the shape of the dose-effect curve. For lethality, V is generally larger than 4 and demonstrates one reason why one would not want to use a linear dose-squared model for early effects. The shape parameter V also seems to have the same value for brief and protracted exposure to low-LET radiation, although this is not a firm conclusion. For alpha emitters, V seems to differ from that for low-LET radiation, indicating that the RBE will change as the dose changes. The hazard function modeling technique used here can accommodate a changing RBE. Although some modifications are required, simultaneous exposure to beta and alpha radiations could be accommodated (Scott, 1983, 1984).

If the shape parameter V is the same for the brief and each of the protracted exposures considered, adding up the increments in the cumulative hazards leads to a simple solution for the total hazard, when considering effects on a single organ. For bone marrow effects, assuming minimal treatment, the total hazard is given by

$$HB = ln(2)\,(D1/3.4 + D2/7 + D3/14)^{10} \quad (1.9)$$

The respective cumulative hazards *HL* and *HGI* are expressed in a similar way for the lung and GI tract. Summing the lethality functions *HB*, *HGI*, and *HL* gives a total *H* for lethality. If this is represented by H_{early}, then the total lethality risk is $1 - \exp - [H_{early}]$.

1.4 Uncertainties in Dose-Response Functions

There are several sources of uncertainty in the dose-response functions developed in this chapter. The major potential sources of uncertainty are: (1) statistical variability in parameter estimates derived from weak (small) data bases; (2) uncertainty in cross-species extrapolation; (3) uncertainty due to inadequate basis for choice of form of dose-response model; (4) problems in accounting for dose-rate dependence of model parameters; (5) impact of sensitive individuals on population dose-response function; and (6) limitations in our understanding of the effects of medical treatment. Here the sources of uncertainty are described and a method for developing approximate bounds for the dose-response functions is presented.

Some of the functions have been developed from analysis of human data. The three main sources of human data are accidents, therapeutic exposures, and the bombing of Hiroshima and Nagasaki. Accidental overexposures commonly involve small numbers of otherwise healthy middle-aged males. Because of the small numbers of people exposed, there are random (Poisson) uncertainties inherent in risk estimates derived from these data. These Poisson uncertainties severely restrict our understanding of the tails of the dose-response function. Because the exposed individuals are typically healthy middle-aged males, uncertainties are introduced when we attempt to predict the risks in mixed populations of adults and children, men and women, and healthy and diseased individuals on the basis of these data. Interpretation of data from accidental overexposure is often further complicated by limited knowledge of the doses and dose rates involved, and by the fact that most accident victims receive extensive individual medical care. Because medical care may influence risk in significant but imprecisely-understood ways, uncertainties are introduced in our estimates of the risk that would be faced by individuals receiving treatment substantially different than that given to accident victims.

Data from human therapeutic exposures have been used to derive some of the dose-response functions. Typically therapeutic data involves larger numbers of subjects, and because of this, Poisson uncertainties tend to be less of a problem. Further, in therapeutic settings the doses are generally well known. However, therapeutic doses are often administered according to schedules that generate patterns of dose and dose rate that are quite different from those expected to follow a nuclear power plant accident. Uncertainties are introduced by our attempts to adjust the parameter estimates obtained from analysis of therapeutic data so they will predict risk in the circumstances of interest. Interpretation of therapeutic data is further complicated by the fact that the individuals irradiated are already sick, may have received previous treatments, and are under the care of a physician. Extrapolation of results from these unusual populations to predict risk in the general population introduces uncertainty.

Data from the survivors of the atomic bombings of Hiroshima and Nagasaki pose somewhat different issues. First, the population that *survived* the bombings may not be

representative of the general population. Second, the dose was received at high dose rate almost instantaneously. Third, the dosimetry is, at this time, somewhat uncertain. The major advantage of this data set is the relatively large number of individuals involved.

Where adequate human data were unavailable, dose-response functions were based upon data from experiments involving animals, typically from inbred colonies of rats or dogs. In these experimental settings, relatively large populations are involved and doses are well known. As a result, it is frequently possible to determine well the dose-response curves appropriate for the experimental animals. However, there is a certain inevitable uncertainty in any extrapolation from one species to another. Depending upon the validity of the analogy, there may be more or less uncertainty involved. A further complication is introduced by the use of inbred laboratory animals — inbreeding reduces heterogeneity and is likely to result in steeper dose-response functions than those likely to be appropriate for heterogeneous human populations.

There is also a question as to which form of dose-response model to fit to the data. And this is a potential source of uncertainty. However, if the dose-effect models used are not extrapolated to risks less than about 5%, the uncertainty due to choice of model will be quite small because of the steepness of the dose-effect curve. Use of any plausible sigmoidal function will lead to about the same estimate of risk above about 5%. When one considers that the population at risk will be exposed to a distribution of doses, with many individuals below the effective threshold dose, a small percentage having doses in the risk range between 5% and 100%, and a somewhat larger group with doses above this range, it is unlikely that model selection will have a major impact on the expected mortalities. All plausible models will predict 100% mortality for those individuals receiving doses above the 100% risk level, and essentially everyone with doses slightly less the the 5% risk level will be predicted to survive, regardless of the model used.

When risks must be projected for protracted exposures at low dose rate there are additional concerns. Uncertainties are potentially introduced by our adjustment of the parameters of dose-response functions to account for low dose rate. However, there is much evidence of a 1/3 power relationship of dose for a specified effect vs exposure time (Lushbaugh, 1982). This 1/3 power relationship is supported by data for the effects of beta irradiation on the lungs that was used to develop the mortality risk estimates used in this chapter (Scott and Seiler, 1984). Because all the D_{50} values and protraction factors used in this chapter were consistent with or were based on this 1/3 power relationship, the uncertainty in accounting dose-rate effects for mortality should be relatively small.

Ideally it would be possible to rigorously develop well-defined estimates of the uncertainty in each dose-response model. One might hope to derive, as a minimum, 5%, 50%, and 95% confidence limits for the LD_5 (ED_5), LD_{50} (ED_{50}), and LD_{95} (ED_{95}).

An approach frequently useful for uncertainty analysis is Monte Carlo simulation. To determine the uncertainty in the risk, R, projected to occur at a level of dose, d, using the hazard function model:

$$R = 1 - e^{-0.693 \left[\frac{d}{D_{50}} \right]^{V}} \tag{1.10}$$

where D_{50} and V are imprecisely known, one would first estimate probability density functions for D_{50} and for V. Once these had been derived, one would randomly draw a set of trial values of D_{50} and V from the probability density functions and calculate the value of R generated by these values. This process would be repeated many times until the full distribution of estimates of R was obtained.

The mathematics of Monte Carlo simulations are relatively straightforward. However, to apply the approach one must obtain estimates of the probability density functions of each variable of interest, here D_{50} and V; and if the parameter estimates are correlated, one must have an estimate of the degree of correlation.

Two approaches were considered for deriving a probability density function for the LD_{50} for bone marrow mortality. First, we attempted to predict the LD_{50} for humans from the data for 14 other species presented in Figure 1.2. A regression of the natural logarithm of the LD_{50} (Gy) on the natural logarithm of body weight (gm) yielded:

$$\ln\left[LD_{50}\right] \approx 2.8 - 0.172 \ln\left[Wt\right] \pm 0.378 \tag{1.11}$$

Evaluating this expression at a typical human body weight of 70 Kg yields an LD_{50} estimate of approximately 2.4 Gy, with 95% confidence intervals spanning a factor of about 2, i.e., 1.2 Gy to 4.8 Gy.

The available data from accidental overexposures were reviewed in an attempt to narrow these confidence intervals. A logistic regression analysis was performed using the data from Smith's (1983) review of 35 individuals with accidental overexposures. This data set includes accident victims from more than ten separate incidents including the relatively recent (1974 and 1977) incidents in New Jersey. Almost all of these individuals received supportive treatment and some received bone marrow transplants. Two individuals who received highly non-uniform exposures were excluded from the analysis. The result was:

$$R = \frac{1}{1 + e^{-(-5.2 + 0.94\,d)}} \tag{1.12}$$

where d is the dose (Gy) and R is the risk of death.

The 26 Ewing's sarcoma patients, reported by Rider and Hasselback (1968) and Millburn and coworkers (1968), were added to the data base and the analysis was repeated.[1] The result was:

$$R = \frac{1}{1 + e^{-(-6.6 + 1.1\,d)}} \tag{1.13}$$

where d is the dose (Gy) and R is the risk of death. These two analyses suggest LD_{50}s for

[1] The original Rider and Hasselback paper mentioned "about 20" cases. In fact, there were 22 cases. Four additional cases are discussed by Millburn *et al.*, 1968.

supportive treatment in the neighborhood of 6 Gy and equivalent hazard function slopes of approximately 3 to 4. The estimates of the LD_{50} and of the shape parameters from these analyses were negatively correlated.

An uncertainty analysis was then conducted to determine how precisely these data identify the LD_{50}. When the variance and covariance of the two parameters of the logistic regression were accounted for, it became evident that these data provide little information about the LD_{50}. A 95% confidence interval (generated by Monte Carlo simulation) for the LD_{50} based on these data alone spanned the region from about 3.5 Gy to well over 10 Gy.

In view of the ambiguities inherent in interpretation of these analyses, we abandoned the formal approach and concentrated instead upon developing approximate upper and lower bounds for the bone marrow syndrome dose-response function.

1.4.1 Minimal Treatment

For minimal treatment the central estimates are obtained using a median lethal dose of 3.4 Gy and a shape parameter of 10. An approximate upper bound for the risk can be found by using a median lethal dose of 2.8 Gy and a shape parameter of 15.[2] The 2.8 Gy value comes from Lushbaugh's (1967) data on one hundred individuals, most with terminal leukemia or inoperable cancer, who received doses between 0.3 and 3.0 Gy. Also included were seven nuclear radiation accident victims. Because of their severe illness, these patients had a relatively high probability of dying even without exposure to radiation. No adjustments were made in Lushbaugh's analysis to account for the deaths expected from pre-existing disease. The 2.8 Gy value is consistent with Baverstock and Ash's (1983) conclusion that the dose required to kill more than a few healthy individuals might not be less than 3 Gy. The shape parameter of 15 is simply 1.5 times the central estimate of 10. The factor of 1.5 represents our best subjective estimate of the uncertainty in the shape parameter. An approximate lower bound for risk can be found by using a median lethal dose of 4.0 Gy and a shape parameter of 6.6.[3] The 4.0 Gy value was constructed by multiplying the central estimate of 3.4 Gy by 1.2, the ratio of the central estimate to the upper bound. Although the symmetry of the upper and lower bounds for the LD_{50} is somewhat arbitrary, the resulting estimate of 4.0 Gy is consistent with Smith's (1983) recommendations. The shape parameter of 6.6 is simply $\frac{1}{1.5}$ times the central estimate of 10.

1.4.2 Supportive Treatment

For supportive treatment the central estimates are obtained using a median lethal dose of 4.5 Gy and a shape parameter of 6.6. The 4.5 Gy estimate is consistent with Mole's (1984) analysis of the data from individuals involved in radiation accidents. Mole's analysis used

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[2] The use of a high value of the shape parameter in conjunction with a low value of the LD_{50} to generate an upper bound, and a low value of the shape parameter in conjunction with a high value of the LD_{50} to generate a lower bound is consistent with the negative correlation between the parameter estimates observed in our data analysis.

[3] The use of a high value of the shape parameter in conjunction with a low value of the LD_{50} to generate an upper bound, and a low value of the shape parameter in conjunction with a high value of the LD_{50} to generate a lower bound is consistent with the negative correlation between the parameter estimates observed in our data analysis.

data for the Vinca, Yugoslavia criticality accident (5 individuals, one dropped from analysis), for the Oak Ridge Y-12 criticality accident (4 individuals, one dropped from analysis), and for the Ewing's sarcoma patients (20 individuals), along with information on the shape of the dose-effect curve for lethality derived from laboratory animal data. All of the exposed individuals received some supportive treatment. As mentioned in section 1.2.2.1, although Mole discounts the importance of the medical treatment, our interpretation is that his estimate of 4.5 Gy is appropriate for patients receiving supportive medical treatment. Basically, Mole's estimate of 4.5 Gy was derived by drawing a line with a coefficient of variation of 10% (approximately equivalent to a shape parameter of 5) through the point dose = 3 Gy, risk = 0.037 on normal probability paper. The dose is the average dose received by the 27 individuals. (This average dose is dominated by the 3 Gy value of the 20 Ewing's sarcoma patients.) The risk of 0.037 is simply 1 death divided by 27 individuals at risk. Our own reanalysis of these same data, under the constraint that the shape parameter was 6.6, yielded a 4.8 Gy LD_{50}. An approximate upper bound for risk after supportive treatment can be found by using the parameters 3.4 Gy and shape = 10, developed as central estimates for minimal treatment. An approximate lower bound for risk can be found using a LD_{50} of 6 Gy and a shape parameter of 4.4. The 6 Gy value was constructed by multiplying the central estimate of 4.5 Gy by 1.33, the ratio of the central estimate to the upper bound. The shape parameter of 4.4 is simply $\frac{1}{1.5}$ times the central estimate of 6.6. Although the symmetry of the upper and lower bounds for the LD_{50} and shape parameter is somewhat arbitrary, both the LD_{50} of 6 and the shape of 4.4 are consistent with our own unconstrained logistic regression analysis of the data on accident victims and patients with Ewing's sarcoma.

1.4.3 Summary

The uncertainty estimates developed above are quite imprecise. However, we feel that they represent the best estimates that can be developed on the basis of available data. The estimates of the LD_{50} for bone marrow mortality vary from 2.8 to 6.0 Gy. This is a large range, but few would argue that appreciable risk would be involved below 3 Gy and yet the data available between 3 and 6 Gy are so sparse that it is conceivable that with supportive treatment half of the population might survive doses as large as 6 Gy.

Unfortunately, limitations in the raw data, inadequacy of theory, and resource constraints combine to severely limit analysis of uncertainty. Because death is more significant than illness, and because most early deaths in the aftermath of a nuclear power plant accident are expected to be caused by injury of the bone marrow, we concentrated on developing uncertainty estimates for death from bone marrow syndrome. No estimates of uncertainty were developed for other causes of death or for nonfatal illnesses. If these are determined to be important contributors to the aggregate health consequences of nuclear power plant accidents, future efforts should be directed toward development of appropriate uncertainty estimates.

1.5 Comparison with Reactor Safety Study Model Approach

In this section, the differences between the median lethal doses developed in this chapter and those used in the Reactor Safety Study (WASH 1400, 1975) are discussed. This includes a comparison of the hazard function modeling approaches used in this chapter with the methods that were used in the Reactor Safety Study to predict the single-organ effects of

brief high dose rate exposure followed by protracted exposure and to predict the effects of multiple organ injuries.

A comparison of median lethal doses for brief and protracted exposure, for each critical organ is provided in Table 1.19. Note that the time periods over which dose protraction was considered differ between the Reactor Safety Study and what was used in this chapter.

In the Reactor Safety Study, dose rate protraction factors associated with the median lethal doses in Table 1.19 were used to add the brief and protracted doses to estimate the lethality risk from injury to the bone marrow, gastrointestinal tract, and lung. A different type of risk function was used for each organ. Also shown are the new sigmoidal risk functions developed in this chapter, based on the Weibull function. Cumulative hazards associated with these curves were used indirectly to calculate risks.

For lethality risks from injury to bone marrow, piece-wise straight-line relationships were plotted on normal probability paper in the Reactor Safety Study and indicate that a complex bimodal Gaussian-type model was used. A unimodal Gaussian model would have been represented by a straight line relationship without a break in the curve. In this report, the bimodal curves used in the Reactor Safety Study have been replaced with unimodal sigmoidal curves (Figure 1.18).

In the Reactor Safety Study, the lower large intestine was considered the critical component of the gastrointestinal tract, based mainly on internal dose considerations. However, for external radiation, the small intestines should have also been considered. For risks of lethal injury to the lower large intestine, a linear threshold (absolute) model was used in the Reactor Safety Study (Figure 1.19). This linear curve has been replaced with two sigmoidal-type curves: One for the small intestines and a second for the lower large intestines. For brief radiation exposure, calculation of risks is based indirectly on the curve for the small intestines. For protracted internal beta irradiation, calculations of risks are based indirectly on the curve for the lower large intestine.

A third type of model was used in the Reactor Safety Study for lethality risks from injury to the lung (Figure 1.20). This consisted of a power-function-type model in which the risk increases in proportion to dose raised to a constant power. The dose-effect curve associated with the model used in the Reactor Safety Study is for a specific dose rate pattern to the lung. In this report, this curve has been replaced with four new curves to accommodate a wider range of dose rate patterns. Calculations of risks are based indirectly on these curves.

To account for dose rate effects on a critical organ, instead of adding the doses, the increments in the cumulative hazard associated with each risk estimator are calculated for brief exposure followed by protracted exposure. These increments are specific for varying time intervals for dose protraction, and they differ for each critical organ. The organ-specific increments are added to obtain cumulative hazards HB, HGI, and HL for mortality from injury to the bone marrow, gastrointestinal tract, and lung.

In the Reactor Safety Study, lethality risks in multiple organ injuries were calculated as follows:

$$\text{Risk} = RB + (1 - RB) \times RL + (1 - RB) \times (1 - RL) \times RGI \qquad (1.14)$$

where RB, RL, and RGI are lethality risk estimates for death from injury to the bone marrow, lung, or gastrointestinal tract, respectively.

Table 1.19 A Comparison of D_{50} Values for Lethality from Early and Continuing Effects Used in the Reactor Safety Study with Those Used in the New Models

Organ	Time Period to Evaluate Dose (Days)		D_{50} (Gy)	
	WASH 1400	New Models	WASH 1400	New Models
Bone Marrow				
Minimal[a]	0-7	0-1	3.4	3.4
Supportive[a]			5.1	4.5
Intensive[a]			10.5	11.0
Minimal	8-30	1-14	7	7
Supportive			10.2	-
Minimal	-	14-30	-	14.0
Gastrointestinal Tract[b]				
	0-1	0-1	35	15
	1-7	1-7	35	35
Lung[c]				
Adults	0-365	0-1	200	9.5
		1-14		94
		14-200		200
		200-365		540
Children	0-365	0-1	200	4.8
		1-14		47
		14-200		110
		200-365		270

[a] Categories of medical treatment as discussed in the text.

[b] Use of a mild laxative can reduce the internal dose to the gastrointestinal tract by a factor of 2-4.

[c] Lung lavage can reduce the internal dose to the lungs by a factor of about 2.

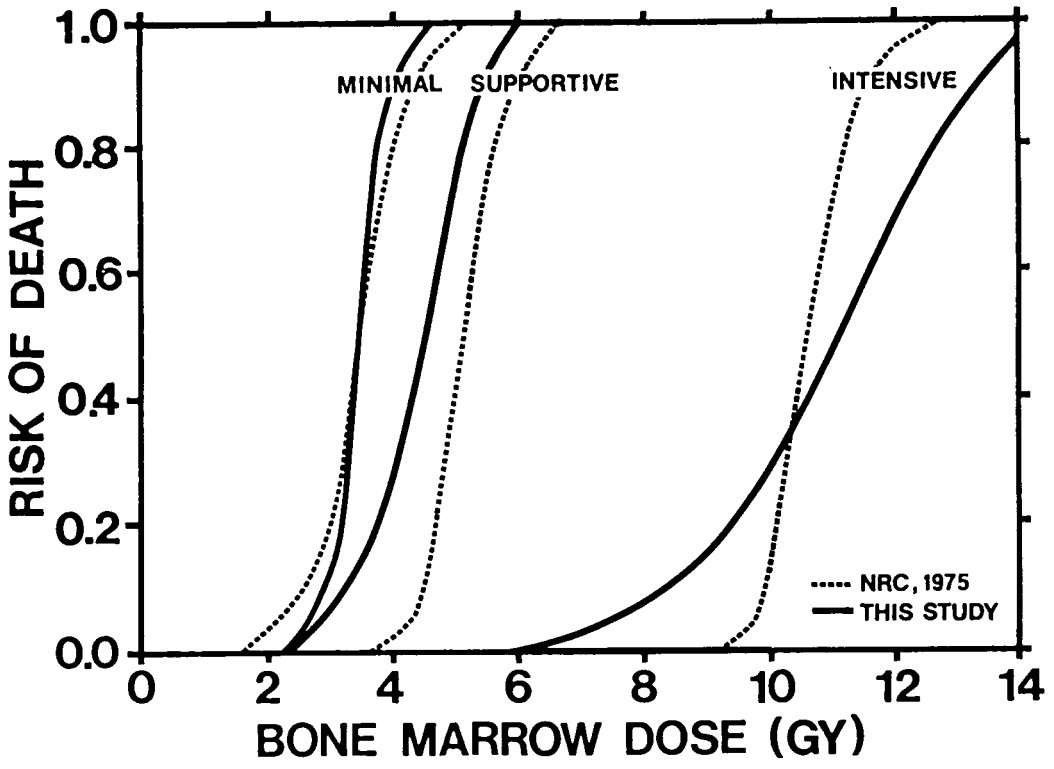

Figure 1.18 Dose-mortality relationships for irradiation of bone marrow; from NRC, 1975, and from this study.

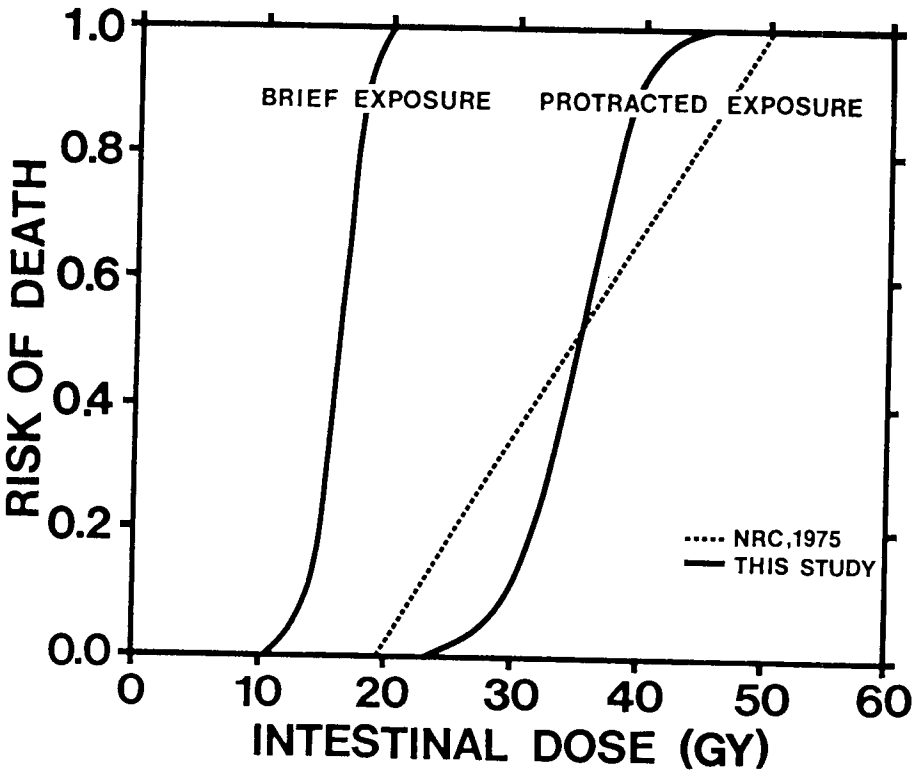

Figure 1.19 Dose-mortality relationships for irradiation of the small intestine or colon, from NRC, 1975, and from this study.

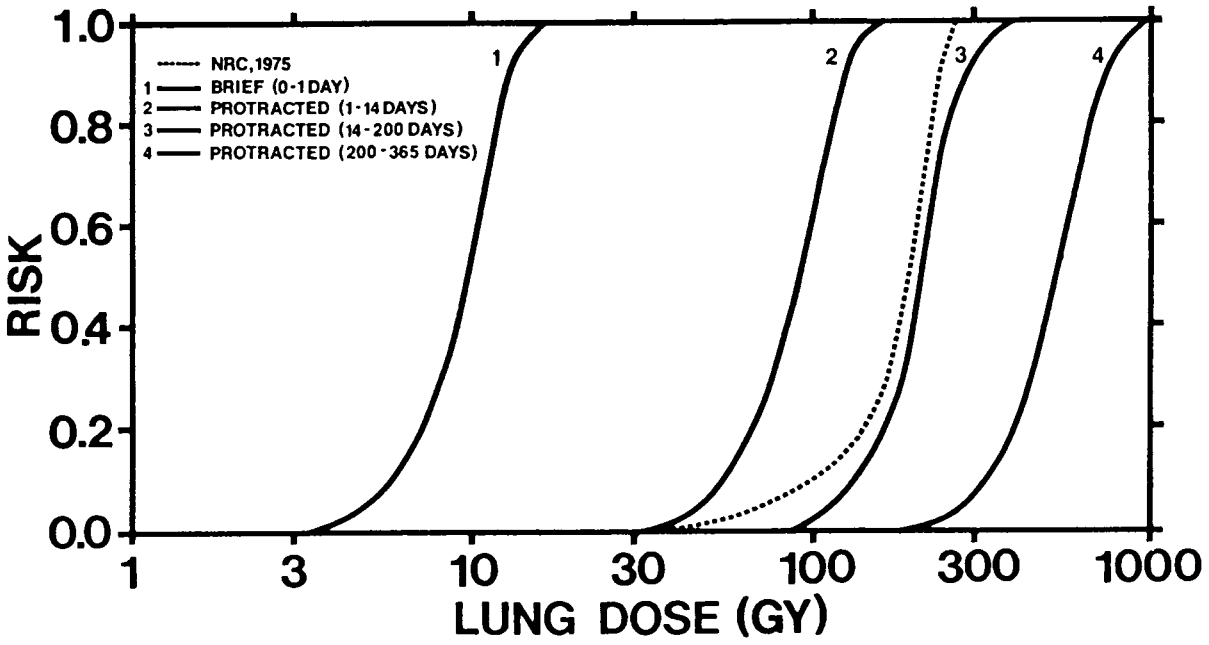

Figure 1.20 Dose-response functions for mortality from pulmonary syndrome criterion used in consequence model. From NRC, 1975, and from this study.

Using a hazard function modeling approach, the complex expression represented by equation (1.14) has been eliminated. Instead of using such an expression, the cumulative hazards *HB*, *HGI*, and *HGI* that correspond to each of these critical organs are simply added to obtain the total hazard H_{early} for lethality from early and continuing effects. The risk, taking into account multiple organ injuries, is then given by

$$\text{Risk} = 1 - \exp\left(-H_{early}\right) \tag{1.15}$$

In the case of gastrointestinal injury, injury to both the small intestine from brief exposure and the large intestines (brief dose and protracted beta doses) are accommodated.

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Chapter 2

LATE SOMATIC EFFECTS

E. Gilbert

Executive Summary

Late effects are by definition effects that occur at least one year, and in most cases decades, after the time of exposure. The late effects considered in this chapter are limited to latent cancer incidence and mortality, and benign thyroid disease.

A model is provided for estimating risks of late effects resulting from the radiation exposure likely to be received in the event of a nuclear power plant accident. It is assumed that exposure to high-LET radiation would be negligible in such an accident, and thus only risks from low-LET exposure are evaluated. Separate estimates are provided for risks of leukemia, bone cancer, lung cancer, gastrointestinal cancers, thyroid cancer, skin cancer, and the residual group of all other cancers; estimates of leukemia and other cancers due to *in utero* exposure are also provided. Risks are expressed in absolute terms as the number of cancer deaths (or cases) per million persons exposed to a particular dose. Because the time of death is also important in assessing the impact of an accident, and because the quality of life after the occurrence of cancer will often be reduced, the number of years of life lost and the number of years of life lived after the occurrence of cancer are also estimated.

Since the publication of the Reactor Safety Study (NRC, 1975), additional epidemiological data for estimating the risk of cancer due to radiation have become available. In updating the material in this earlier report, we have made extensive use of the BEIR III report of the National Academy of Sciences (1980), including the updated cancer mortality and incidence data on the Japanese atomic bomb survivors. It is important to note, however, that we have not attempted to speculate regarding the effects on risk estimates of the current reassessment of the doses received by the Japanese survivors; thus, the numerical estimates provided in this report must be reevaluated when analyses based on revised atomic bomb dosimetry become available.

Consideration of these additional data have led to a number of modifications of the model used in the earlier Reactor Safety Study (NRC, 1975). The most important of these are that risks for cancers other than leukemia and bone are assumed to persist for a lifetime (rather than 30 years), and that the relative risk projection model has been used in several instances. Other important changes are that numerical risk coefficients have been revised and, as previously mentioned, estimates of years of life lost are provided.

Because there is considerable diversity of opinion among the scientific community, three sets of estimates are given, central, as well as upper and lower estimates. The central estimates are intended to reflect the most realistic assessment of radiation risks based on the collective judgment of the Advisory Committee and others involved in the preparation of this report, as determined from evidence available at the time of its preparation. The upper and lower bounds are intended to reflect alternative assumptions that are also reasonably consistent with available evidence. The upper (lower) estimates should not be considered as resulting from the set of assumptions that would lead to the highest (lowest) possible estimates. These bounds also cannot be regarded as confidence limits since it is not feasible to associate a level of probability with them.

The upper bounds are based on a linear model, while, in most cases, the central estimates and lower bounds are obtained by modifying the linear estimates by a factor intended to account for the reduced effectiveness of exposure at low doses and dose rates. Both absolute and relative risk models are used for obtaining lifetime linear risk estimates, but in both cases the lifetime risk estimates are obtained by applying estimates of annual risk over a

specified time period following exposure. The annual risk coefficients were obtained from epidemiological data on several populations including the Japanese atomic bomb survivors and several groups that have been exposed to radiation for therapeutic reasons. Both annual and lifetime risk estimates are based on estimated organ dose.

With the absolute risk model, risk coefficients are expressed as the number of deaths (or cases) per 10^4 person-year (PY) per Gy. To obtain lifetime risk estimates, these coefficients are multiplied by the number of person-years at risk as calculated using a life table method that takes into account attrition of the population from mortality unrelated to radiation exposure. With the relative risk model, the risk coefficients are expressed as a percent-per-Gy increase in the risk from spontaneous cancers. To obtain lifetime relative risk estimates, these coefficients are multiplied by the number of spontaneous cancers expected (based on U.S. incidence and mortality rates) during the period of risk. As mentioned previously, the number of years of life lost and the number of years of life lived after the occurrence of cancer, based on each of the two models, have also been calculated.

For leukemia and bone cancer, risks are assumed to persist for a period of 2 to 27 years following exposure. An absolute risk model is used to determine the age distribution of the resulting deaths. For other cancer sites, risks after a specified latent period are assumed to persist for a lifetime. This latent period is assumed to be five years for thyroid cancer, and ten years for all other effects. Both relative and absolute models are considered for projecting risks beyond the period for which follow-up data are available, as described above. For exposure received *in utero,* risks are assumed to persist for a period of 0 to 12 years after birth for leukemia, and 0 to 10 years after birth for other cancers, with the absolute risk model used to determine the age distribution of these deaths.

Because of the difficulty in obtaining reliable estimates for those who are young at exposure, in most cases a single risk coefficient based on combined data for all exposure ages has been used to calculate lifetime risks. Exceptions to this approach are thyroid cancer and the upper bound estimates for breast cancer, where separate estimates are used for those under and over age 20 at exposure. Effects of exposure received *in utero* are also estimated separately.

The upper bound estimates are the linear estimates calculated as described above without modification for low doses or dose rates. Upper bound estimates for lifetime risks of mortality from several cancer types are presented in Table 2.0. The use of the linear model has generally been considered to be conservative for estimating effects of exposure to low-LET radiation since experiments with animals indicate that a linear-quadratic function provides a more realistic description of the dose-response relationship (UNSCEAR, 1977; BEIR III, 1980; NCRP, 1980). With the exception of leukemia, bone cancer, skin cancer, thyroid disease, and all cancers resulting from exposure received *in utero,* the upper bound is based on the relative risk model. The upper bound for breast cancer differs from the central estimate in that age at exposure is taken into account. For lung cancer, a larger relative risk coefficient is used for the upper bound than for the central estimate, a procedure intended to reflect the uncertainty in extrapolating to the United States population an estimate based primarily on Japanese data.

For most cancer types, the central estimates are obtained by modifying the linear risk estimates by the factor $0.30 + 0.47\ D$ (where D is the dose in Gy), resulting in a linear-quadratic function of dose. The intent of using this factor is to account for the reduction of

Table 2.0 **Central Estimates (With Upper and Lower Bounds) For Lifetime Risks of Mortality Resulting From** Low-LET Exposure Received at Low Dose Rates (<0.05 Gy Per Day) Based on the Linear Term of the Linear Quadratic Function

Effect	Number of Deaths ($Per\ 10^4$ Per Gy)			Years of Life Lost ($Per\ 10^4$ Per Gy)		
	Lower Bound	Central Estimate	Upper Bound	Lower Bound	Central Estimate	Upper Bound
Cancers Due to Other Than *In Utero* Exposure						
Leukemia	5	14	48	168	505	1682
Bone	0.2	1	2	7	22	75
Breast	4	60	87	97	955	1452
Lung	5	20	138	100	288	1971
Gastrointestinal	9	57	189	222	661	2202
Thyroid	7	7	7	20	203	203
Other	5	29	96	124	378	1260
Cancers Due to *In Utero* Exposure						
Leukemia	1.2	1.2	3	80	80	200
Other	1.2	1.2	3	80	80	200

effects likely to result from the low doses and dose rates expected to be experienced by much of the exposed population in a nuclear power plant accident. The factor 0.30 is obtained as the midpoint of the range 0.1 to 0.5 suggested by NCRP (1980). The 0.47 value is chosen so that $0.30 + 0.47\ D$ will be unity at 1.5 Gy (150 rad). The factor is applied only for doses under 1.5 Gy. For doses received at low dose rate (< 0.05 Gy/day) effects are modified by the factor 0.30 (that is, the quadratic term is not used). Exceptions to the use of these reduction factors in obtaining central estimates are breast cancer, thyroid cancer, and cancers resulting from *in utero* exposure. For breast cancer, the non-age-specific linear estimate is used without modification for the central estimate. For *in utero* exposure, a lower risk coefficient is used for the central estimate. For leukemia, bone cancer, skin cancer, thyroid disease, and cancers resulting from exposure *in utero,* central estimates are based on the absolute risk model. For all other cancer sites central estimates are based on the relative risk model.

Because the central estimates for most cancer types are not based on a linear model, it is not possible to present lifetime risk estimates per Gy in the manner of the upper estimates. However, in Table 2.0 we have indicated the mortality estimates that would result from the reduction factor 0.30. For low doses (less than 0.1 Gy), expected to predominate in most accident scenarios, the actual factor to be applied ($0.30 + 0.47\ D$) is very close to 0.30.

With the exception of thyroid cancer and cancers resulting from *in utero* exposure, the lower bound estimates are obtained by modifying the linear estimates based on the absolute risk model by the factor $0.10 + 0.60\ D$ (where D is the dose in Gy). The factor 0.10 is obtained as the lowest value of the range 0.1 to 0.5 suggested by NCRP (1980), while the value 0.60 is chosen such that $0.10 + 0.60\ D$ will be unity at 1.5 Gy (150 rad). The factor is applied only for doses under 1.5 Gy (150 rad). For doses received at a low dose rate (< 0.05 Gy/Day), effects are modified by 0.10. It is noted that although the possibility that an effect might not be detrimental (in fact, it might even be beneficial) cannot be excluded at very low doses and dose rates, these possibilities have not been incorporated into the calculation of the lower bound estimates. The lower estimates, based on the limiting reduction factor 0.10, are given in Table 2.0.

2.1 Introduction

Late effects are by definition effects that occur at least one year, and in most cases decades, after the time of exposure. The late effects considered in this document are limited to latent cancer mortality and incidence, and benign thyroid disease. Because many other factors are involved in the causation of these effects, it is not possible to predict that any given individual will develop cancer or other disease as a result of exposure; only the probability or risk can be estimated.

This chapter provides a model for estimating risks of late effects resulting from the radiation exposure likely to be received in the event of a nuclear power plant accident. It is assumed that exposure to high-LET radiation would be negligible in such an accident, and thus only risks from low-LET exposure are evaluated. Risks are expressed in absolute terms as the number of cancer deaths (or cases) per million persons exposed to a particular dose. Because the time of death is also important in assessing the impact of an accident, and because the quality of life after the occurrence of cancer will often be reduced, the number of years of life lost and the number of years of life lived after the occurrence of cancer are also estimated.

The determination of risk estimates requires developing a model by making assumptions about such issues as the shape of the dose-response function, the effect of age at exposure, and the appropriate method for extrapolating forward in time. The choice of assumptions as well as the determining of numerical values to be used in the model requires evaluating data from several sources that are sometimes in conflict and are frequently too week to provide definitive answers to the questions of interest. Different scientists may interpret the same data in different ways, and may also differ in the relative weight given to evidence from different studies. In many cases, cogent arguments can be made for assumptions other than those made in developing the models used in this report.

Because there is considerable diversity of opinion among the scientific community, three sets of estimates are given, central, as well as upper and lower estimates. The central estimates are intended to reflect the most realistic assessment of radiation risks based on the collective judgment of the Advisory Committee and others involved in the preparation of this report, as determined from evidence available at the time of its preparation. The upper and lower bounds are intended to reflect alternative assumptions that are also reasonably consistent with available evidence. The upper (lower) estimates should not be considered as resulting from the set of assumptions that would lead to the highest (lowest) possible estimates. These bounds also cannot be regarded as confidence limits since it is not feasible to associate a level of probability with them.

The recent BEIR III report of the National Academy of Sciences (1980) has been used extensively in determining the models and estimates set forth for this document. The Reactor Safety Study (1975) made extensive use of the BEIR I report, an earlier report of the National Academy of Sciences (1972). The 1980 BEIR III committee used results of epidemiological studies of radiation effects that had become available since the publication of the 1972 BEIR I report, and the resulting models developed are somewhat more complex than those used by the BEIR I committee. Many of the changes in moving from BEIR I to BEIR III have been incorporated into the model presented here. Other reports by a United Nations Committee (UNSCEAR 77) (1977) and by the International Commission on Radiological Protection (ICRP 26) (1977) have also been considered.

Some modification of the BEIR III models has been required. The BEIR III report was primarily concerned with the calculation of risk estimates for overall cancer mortality and incidence resulting from whole-body irradiation. Because a portion of the exposure received in a nuclear power plant accident would be due to inhalation and ingestion of radioactive materials, and because a variety of radionuclides may be released, some organs (the lungs, for example) may receive much higher doses than others. In order to accommodate this nonuniform dose distribution it is necessary to estimate cancer risks on an organ-specific basis. In addition, the BEIR III committee did not directly address the estimation of risks from the range of doses and dose rates likely to be experienced in a nuclear power plant accident.

Since the publication of BEIR III, studies of the Japanese atomic bomb survivors in Hiroshima and Nagasaki have been updated to include an additional four years of follow-up. In formulating our models and estimates, we have attempted to use both updated mortality data from the Japanese Life Span Study (Kato and Schull, 1982) and updated incidence data from the Nagasaki Tumor Registry (Wakabayashi *et al.*, 1983).

Also since the publication of BEIR III, the dose estimates used in the Japanese studies have been seriously challenged by Loewe and Mendelsohn (1981) and Kerr (1981). Studies are now in progress to determine new dose estimates. It is expected that as a result of these studies both air dose estimates in the two cities, and procedures for estimating the attenuating effects of various shielding materials, will be modified. Because the dose reassessment is not yet complete, we do not believe it is appropriate to speculate in this report concerning the effects of revised dosimetry on estimates based on the Japanese data. Thus we have used only the current T65 dosimetry as described and used by Kato and Schull (1982), Wakabayashi *et al.* (1983), and Kerr (1979). These estimates must be reevaluated when analyses based on revised atomic bomb dosimetry become available. Jablon (1984) has noted that the likely effect of the revision will be to increase risk estimates based on the T65 dosimetry by a factor in the neighborhood of two.

However, one effect of the dose revision that has already been established is that neutron dose estimates for the Hiroshima survivors will be greatly reduced, while gamma dose estimates will be increased, accounting for effects previously attributed to neutrons. Since radiation in both cities was predominantly gamma, risk estimates based on data from both cities combined are now more appropriate than previously.

2.2 Summary of the Model

A detailed discussion of the assumptions that have been made in defining the model used for estimating lifetime risks is given in Section 2.3. A summary of the model in tabular form is given in Table 2.1.

For each cancer site considered, three lifetime risk estimates are determined: a central estimate, an upper bound, and a lower bound. The upper bound estimates are based on a linear model, while, in most cases, the central estimates and lower bounds are obtained by modifying the linear estimates as described in Sections 2.2.1 and 2.2.3.

Two models are used for obtaining lifetime linear risk estimates, but in both cases the lifetime risk estimates are obtained by applying estimates of annual risk over a specified time period following exposure. These annual risk coefficients, which are shown in Tables 2.2 and 2.3, are obtained from epidemiological data as described in Section 2.4. Both annual and lifetime risk estimates are based on estimated organ dose.

Table 2.1 Summary of the Model Used to Determine Upper Bound, Central, and Lower Bound Lifetime Risk Estimate for Mortality and Incidence[a,b]

Effect	Risk Estimation Model		
	Upper Bound	Central	Lower Bound
Cancers Due to Other Than In Utero Exposure			
Leukemia	Use absolute linear estimate	Modify upper bound by central estimate reduction factors in Table 2.4	Modify upper bound by lower bound reduction factors in Table 2.4
Bone			
Breast	Use age-specific relative linear estimate	Use non-age-specific relative linear estimate	Modify non-age specific absolute linear estimate by lower bound reduction factors in Table 2.4
Lung	Use relative linear estimate based on a risk coefficient of 37% per Gy	Modify relative linear estimate based on a risk coefficient of 18% per Gy by central estimate reduction factors in Table 2.4	Modify absolute linear estimate by lower bound reduction factors in Table 2.4
Gastrointestinal	Use relative linear estimate	Modify upper bound by central estimate reduction factors in Table 2.4	Modify absolute linear estimate by lower bound reduction factors in Table 2.4
Thyroid[c]	Use absolute linear estimates	Use absolute linear estimate	Use absolute linear estimate
Skin	Use absolute linear estimate	Modify upper bound by central estimate reduction factors in Table 2.4	Modify upper bound by lower bound reduction factors in Table 2.4
Other Cancers	Use absolute linear estimates	Modify upper bound by central estimate reduction factors in Table 2.4	Modify absolute linear estimate by lower bound reduction factors in Table 2.4
Benign Thyroid Nodules[d]	Use absolute linear estimate	Use absolute linear estimate	Use absolute linear estimate
Cancers Due To In Utero Exposure	Use absolute linear estimates	Use absolute estimates multiplied by 0.4	Use central estimates

[a] The linear estimates referred to are given in Table 2.2 (mortality) and Table 2.3 (incidence).

[b] For convenience, "linear lifetime risk estimates based on the absolute (relative) risk model" are referred to as "absolute (relative) linear estimates."

[c] ^{131}I is assumed to be as effective as external radiation for the upper bound thyroid cancer, one third as effective for the central estimate, and one tenth as effective for the lower bound (see section 2.4.6).

[d] ^{131}I is assumed to be as effective as external radiation for the upper bound thyroid nodules, and one fifth as effective for the central estimate and lower bound (see section 2.4.6).

Table 2.2 **Risk Coefficients And Lifetime Linear (Upper Bound) Risk Estimates For Mortality From Several Cancer Types**

Effect	Risk Coefficients: Absolute (Per 10^4 PY Per Gy)	Risk Coefficients: Relative (% Per Gy)	Period Assumed To Be At Risk (Years Following Exposure)	Number Of Deaths[a] (Per 10^4 Per Gy): Absolute[b]	Number Of Deaths[a] (Per 10^4 Per Gy): Relative[b]	Years Of Life Lost[a] (Per 10^4 Per Gy): Absolute[b]	Years Of Life Lost[a] (Per 10^4 Per Gy): Relative[b]
Cancers Due To Other Than In Utero Exposures							
Leukemia[c]	2.24	-	2-27	48	-	1682	-
Bone	0.1	-	2-27	2	-	75	-
Breast							
Age-specific	3.5[d,e], 2.3[d,e]	103[d], 42[d]	10 to end of life	47[f]	87[f]	1102[f]	1452[f]
Non-age-specific	2.6[e]	45		43[f]	60[f]	973[f]	955[f]
Lung	2.0 -	18[g] 37[g]	10 to end of life	53 -	67 138	999 -	959 1971
Gastrointestinal	2.7	39	10 to end of life	91	189	2223	2202
Thyroid	0.25[d,e], 0.125[d,e]	-	5 to end of life	7	-	203	-
Other (excluding types above plus skin and prostate)	1.5	20	10 to end of life	50	96	1235	1260
Cancers Due To In Utero Exposures[c]							
Leukemia	25[h]	-	0-12	3[i]	-	200[i]	-
Other	28[h]	-	0-10	3[i]	-	200[i]	-

[a] **These risks are based on a linear model and in most cases must be modified as described in Section** 2.2.1 **and as summarized in Table** 2.1 **to obtain central and lower bound estimates.**

[b] **Estimates based on the absolute (relative) risk projection models described in Section** 2.3.2.

[c] **These estimates may be too high because of recent improvements in cure rates (see Section** 2.3.3).

[d] **In each case, the first coefficient is for those under age 20 at exposure while the second coefficient is for those age 20 and over at exposure.**

[e] **The absolute risk coefficients are obtained by reducing the incidence coefficients (Table** 2.3) **as described in Sections** 2.3.3 **and** 2.6

[f] **These are lifetime risk estimates for the entire population and are one-half the risks for females only.**

[g] **The risk estimate based on 18% is used for the central estimate, and that based on 37% is used for the upper bound. (See Section** 2.4.4 **and Table** 2.1).

[h] These risk coefficients apply to the in utero population only.

[i] The lifetime risks apply to the entire population and are about 1% of the risk restricted to the in utero population.

Table 2.3 Risk Coefficients And Lifetime (Upper Bound) Risk Estimates For Incidence From Several Cancer Types

Cancer Type	Risk Coefficients: Absolute[d] Per 10^4 Per Py Gy	Risk Coefficients: Relative (% Per Gy)	Period Assumed To Be At Risk (Years Following Exposure)	Number of Cases[a] (Per 10^4 Per Gy): Absolute[b]	Number of Cases[a] (Per 10^4 Per Gy): Relative[b]	Years Of Life Lived With Cancer Per 10^4 Per Gy: Absolute[a]	Years Of Life Lived With Cancer Per 10^4 Per Gy: Relative[b]
Breast							
Age-specific	10.4[c], 6.6[c]	103[c], 42[c]	10 to end of life	137[e]	254[e]	2132[e]	3204[e]
Non-age-specific	7.4	45	10 to end of life	122[e]	172[e]	1796[e]	2057[e]
Lung	2.2[d] -	18[f] 37[f]	10 to end of life	58 -	74 152	100 -	129 265
Gastrointestinal	4.6[d]	39	10 to end of life	155	322	1564	1719
Thyroid	2.5[c], 1.25[c]	-	5 to end of life	72	-	2026	-
Skin	2.0	-	10 to end of life	67	-	1635	-
Other (excluding types above plus skin, prostate, leukemia, and bone)	2.9[d]	20	10 to end of life	98	187	1152	1530
Benign Thyroid Nodules	9.3[c], 4.7[c]	-	10 to end of life	268	-	-	-

[a] These risks are based on a linear model and in most cases must be modified as described in Section 2.2.1 and as summarized in Table 2.1 to obtain central and lower bound estimates.

[b] Estimates based on the absolute (relative) risk projection models described in Section 2.3.2.

[c] In each case, the first coefficient is for those under age 20 at exposure while the second coefficient is for those age 20 and over at exposure.

[d] These absolute risk coefficients are obtained as described in Sections 2.3.3 and Section 2.6.

[e] These are lifetime risk estimates for the entire population and are one-half the risk for females only.

[f] The risk estimate based on 18% is used for the central estimate, and that based on 37% is used for the upper bound. See Section 2.4.4 and Table 2.1.

With the absolute risk model, risk coefficients are expressed as the number of deaths (or cases) per 10^4 per person-year (PY) per Gy. To obtain lifetime risk estimates, these coefficients are multiplied by the number of person-years at risk as calculated using a life table method that takes into account attrition of the population from mortality unrelated to radiation exposure. With the relative risk model, the risk coefficients are expressed as a percent increase per Gy in the risk from spontaneous cancers. To obtain lifetime relative risk estimates, these coefficients are multiplied by the number of spontaneous cancers expected (based on U.S. mortality and incidence rates) during the period of risk. The number of years of life lost and the number of years of life lived after the occurrence of cancer, based on each of the two models, can also be calculated. Additional discussion of the relative and absolute risk models is given in Section 2.3.2; details regarding calculations are given in Section 2.6.

For leukemia and bone cancer, risks are assumed to persist for a period 2 to 27 years following exposure. An absolute risk model is used to determine the age distribution of the resulting deaths. For other cancer sites, risks after a specified latent period are assumed to persist for a lifetime. This latent period is assumed to be five years for thyroid cancer, and ten years for all other effects. Both relative and absolute models are considered for projecting risks beyond the period for which follow-up data are available, as described briefly above and in more detail in Sections 2.3.2 and 2.6.

Because of the difficulty in obtaining reliable estimates for those who are young at exposure, in most cases a single risk coefficient based on combined data for all exposure ages has been used to calculate lifetime risks. Exceptions to this approach are thyroid cancer and the upper bound for breast cancer, where separate estimates for those under and over age 20 at exposure are used. The effect of age at exposure is discussed in Section 2.3.5.

2.2.1 Central Estimates for Latent Cancer Mortality and Incidence

For most cancer types, the central estimates are obtained by modifying the linear risk estimates presented in Tables 2.2 and 2.3 by the factor $0.30 + 0.47\ D$ (where D is the dose in Gy), resulting in a linear-quadratic function of dose. The intent of using this factor is to account for the reduction of effects likely to result from the low doses and dose rates expected to be experienced by much of the exposed population in a nuclear power plant accident. The factor 0.30 is obtained as the midpoint of the range 0.1 to 0.5 suggested by NCRP (1980) while the factor 0.47 is obtained as the value such that the factor will be unity at 1.5 Gy (150 rad). Further discussion of these choices is given in Section 2.3.1. The factor is applied only for doses under 1.5 Gy. For doses received at a rate less than 0.05 Gy (5 rad) per day, effects are modified by the factor 0.30 (that is, the quadratic term is not used). Exceptions to the use of these reduction factors in obtaining central estimates are breast and thyroid cancer. For breast cancer, the non-age-specific linear estimate is used without modification for the central estimate.

For leukemia, bone cancer, skin cancer, and thyroid disease, central estimates are based on the absolute risk model. For all other cancer sites, central estimates are based on the relative risk model. For cancer of the lung and breast, there is reasonably good evidence suggesting that the relative risk model is more appropriate than the absolute risk model (see Sections 2.3.2, 2.4.2, and 2.4.3). However, for gastrointestinal cancers and the residual group of cancers not noted above, the choice is less clear, and while as noted above relative risk is used here, for some purposes it may be appropriate to consider estimates based on the absolute

risk model.

2.2.2 Upper Bound

The upper bound estimates are the linear estimates without modification for low doses or dose rates. The use of the linear model has generally been considered to be conservative for estimating effects of exposure to low-LET radiation since experiments with animals indicate that a linear-quadratic function provides a more realistic description of the dose-response relationship (NCRP, 1980; BEIR III, 1980; UNSCEAR 77, 1977). With the exception of leukemia, bone cancer, skin cancer, and thyroid disease, the upper bound is based on the relative risk model. The upper bound for breast cancer differs from the central estimate in that age at exposure is taken into account. For lung cancer, a larger relative risk coefficient is used for the upper bound than for the central estimate, a procedure intended to reflect the uncertainty in extrapolating to the United States population an estimate based on Japanese data. These choices are discussed in the sections on breast (Section 2.4.3) and lung (Section 2.4.4) cancer.

2.2.3 Lower Bound

To obtain lower bounds, the linear estimates based on the absolute risk model are modified by the factor $0.10 + 0.60\ D$ (where D is the dose in Gy). The factor 0.10 is obtained as the lowest value of the range 0.1 to 0.5 suggested by NCRP (1980), while the factor 0.60 is obtained as the value such that the factor will be unity at 1.5 Gy (150 rad). The factor is applied only for doses under 1.5 Gy (150 rad). For doses received at a rate less than 0.05 Gy (5 rad) per day, effects are modified by the factor 0.10.

It is noted that, although the possibility of no detrimental effect, or even a beneficial effect, cannot be excluded at very low doses and dose rates, these possibilities have not been incorporated into the calculation of the lower bounds.

2.3 Detailed Description of the Model

The various problems that are encountered in attempting to estimate risks due to exposure to low levels of radiation are discussed in detail throughout the BEIR III report. They are briefly summarized in the quotation below of a portion of a paragraph from that report (pp. 142-143).

> The quantitative estimation of the carcinogenic risk of low-dose, low-LET radiation is subject to numerous uncertainties. The greatest of these concerns the shape of the dose-response curve. Others pertain to the length of the latent period, the RBE for fast neutrons and alpha radiation relative to gamma- and x-radiation, the period during which the radiation risk is expressed, the model used in projecting risk beyond the period of observation, the effect of dose rate or dose fractionation, and the influence of differences in the natural incidence of specific forms of cancer. In addition, uncertainties are introduced by the characteristics of the human experience drawn on for the basic risk factors, e.g., the effect of age at irradiation, the influence of any disease for which the radiation was given therapeutically, and the influence of length of follow-up.

The BEIR III committee goes on to note that since many of these uncertainties reflect subjective judgments, it is difficult if not impossible to quantify the collective influence of these uncertainties in a probabilistic sense.

2.3.1 Effects of Low Doses and Dose Rates

Most of the radiation exposure resulting from a nuclear power plant accident is from low-LET radiation and would be received at relatively low doses and dose rates. Because risks are so low in populations exposed at these levels and rates, extremely large sample sizes are required to estimate the magnitude of effects reliably in such populations. In the judgment of the BEIR III committee, none of the studies of human populations that have been exposed primarily at low levels provide sufficient information for risk estimation. Thus it is necessary to extrapolate from estimates based on data from populations which include persons exposed at relatively high doses and dose rates, such as the Japanese atomic bomb survivors and British ankylosing spondylitis patients who were treated with irradiation.

There are many possible functions for describing the dose response relationship for extrapolating from high dose data to low doses; these include the linear function $(\alpha_0 + \alpha_1 D)$, the linear-quadratic function $(\alpha_0 + \alpha_1 D + \alpha_2 D^2)$, and the pure quadratic function $(\alpha_0 + \alpha_2 D^2)$, as well as nonlinear functions with downward curvature $(\alpha_0 + \alpha_3 D^v,\ v < 1)$. These functions are illustrated in Figure 2.1. Data from human populations have thus far proved inadequate to differentiate statistically among plausible dose response functions for extrapolating from high to low doses, or from high to low dose rates. Therefore, the selection of a model must be based largely on data from animal experiments and on theoretical considerations.

Although the BEIR I committee based their estimates on a linear model, additional data and advances in radiobiology led the BEIR III committee to adopt a linear-quadratic function as providing the most plausible description of the dose-response relationship for whole body low-LET radiation in the low to intermediate range. The BEIR III committee also provided alternative estimates based on the linear and pure quadratic models. The use of a model (such as the linear-quadratic) that provides for a reduction in linear effects with low-LET radiation for reduced doses and dose rates can be justified based on experimental evidence that is summarized in a report of the National Council on Radiation Protection and Measurements (1980). In this report it is stated that "it is clear from the data obtained from all endpoints examined, from cell death to tumor induction, that a reduction in dose rate in general results in a reduced biological effect".

Although there seems to be general agreement that for low-LET radiation, low doses and dose rates will result in the reduction of effects, the extent of this reduced effectiveness is not readily quantified. The NCRP report (1980) suggests that effects should be reduced by multiplying by a factor in the range of 0.1 to 0.5 when the dose is less than 0.2 Gy (20 rad) or the dose rate is 0.05 Gy (5 rad) per year or less. In UNSCEAR 77, it is suggested that effects at low doses and dose rates may need to be modified by a factor between 0.25 and 0.50. To obtain the central estimate for latent cancer fatalities in the earlier Reactor Safety Study (1975), effects were modified by a factor of 0.2 for doses less than 0.01 Gy (10 rad) (or dose rates below 0.01 Gy [1 rad]/day), of 0.4 for doses between 0.1 and 0.25 Gy (10 and 25 rad) (or dose rates between 0.01 Gy [1 rad]/day and 0.1 Gy [10 rad]/day), and a factor of 1.0 for other exposures. The use of such factors leads to a discontinuous dose response function. In this

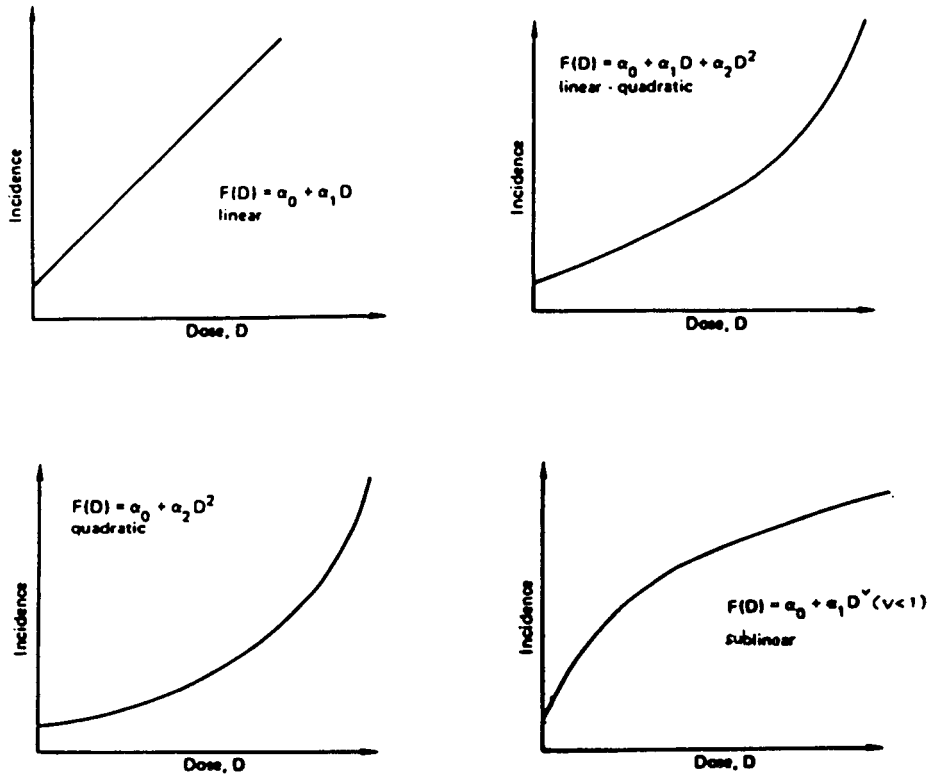

Figure 2.1 Alternate dose-response curves. (BEIR III (1980) Figure II-2 with modifications).

report, we use a reduction factor for low-LET radiation that increases with dose and that is of the form $a+cD$ where D indicates dose. If the linear estimate of the effect being modified is bD, the resulting estimate would be $(a+cD)bD$, which is, of course, a linear-quadratic function. With this approach, a can be thought of as the reduction factor appropriate for very low exposures while c can be determined so that $a+cD=1.0$ for some specified dose D.

Epidemiological and experimental data are not adequate to allow estimation of the parameters a and c for each cancer site of interest. The approach of the BEIR III committee was to utilize data on Japanese survivors to estimate linear and linear-quadratic dose response functions for leukemia and for all cancers other than leukemia. For leukemia, the linear risk estimate per 10^4 person-years given in BEIR III is $2.24D$, where D is the dose in Gy. The linear quadratic risk estimate is $0.99\ D + 0.85\ D^2 = (0.44 + 0.38\ D)2.24D$ so that in the notation of the previous paragraph, $a=0.44$ and $c=0.38$. Similar fits for cancers other than leukemia yield $a=0.40$ and $c=0.35$. The fact that these values are so similar to those obtained for leukemia can be explained by the constraints that were put on the estimates of functions for all cancers other than leukemia.

The linear-quadratic dose reduction factors of BEIR III and the dose-rate reduction factors of NCRP can both be utilized to determine a if it is assumed (NCRP, 1980) that the slopes of the dose-response curves for high dose rates and low dose rates are equal at low doses. Thus the approach used in this report to determine the central estimates for most cancer sites (breast and thyroid cancers are exceptions) is to choose a as the dose-rate reduction factor, or the limiting slope of the linear-quadratic function as the dose approaches zero, and to choose c so that the expression $a + cD$ is equal to unity for some specified D. We have taken $a = 0.3$ and $c = 0.47$, allowing $a + cD$ to reach unity at 1.5 Gy (150 rad) (for doses exceeding 1.5 Gy, a factor of 1.0 is used). The value 0.3 is the midpoint of the range 0.1 to 0.5 suggested by the NCRP and slightly lower than the values used in BEIR III. The value 1.5 Gy is approximately the dose at which the linear and linear-quadratic functions used by BEIR III intersect, and is also the lower bound of the "high dose range" delineated by NCRP (1980). The factor is slightly larger than those used in the Reactor Safety Study (1975) for doses below 0.25 Gy (25 rad), but smaller for doses between 0.25 and 1.50 Gy (25 and 150 rad).

It is expected that habitation of contaminated areas would be permitted only if dose rates were very low, i.e., $<<$ 0.05 Gy (5 rad) per day. Therefore a reduction factor of 0.3 has been applied in our calculations to all chronically received doses (e.g., chronic groundshine). On the other hand, most of the dose received immediately after the accident (e.g., cloudshine) is likely to occur at quite high dose rates, i.e., $>>$ 0.05 Gy (5 rad) per day. Therefore the quadratic term has been included in evaluating risk from any dose received acutely.

Although the linear-quadratic model provides reasonable risk estimates for most cancer sites, other choices such as a linear function cannot be ruled out based on available epidemiological data. Even though animal and other experimental data strongly suggest that some reduction of effects is likely with reduction of doses and dose rates, human populations are considerably more diverse than populations of other animals (especially those used in laboratory experiments) both genetically and with respect to other potential carcinogenic exposures. Thus estimates based on a linear model are also presented, as was done in the BEIR III report. The linear estimates are used to provide an upper bound, while a lower bound for

most sites is based on an alternative linear-quadratic function based on the lowest value of 0.1 suggested by the NCRP. That is, $a = 0.1$ and $c = 0.60$, which allows $a + cD$ to reach unity at 1.5 Gy (150 rad). For doses exceeding 1.5 Gy, the linear function bD is used.

In BEIR III, a pure quadratic is used to provide a lower bound. One of the arguments in support of the quadratic model has been based on differences in the dose-response curves between Hiroshima and Nagasaki. This argument has been weakened by the previously mentioned expected revisions in T65 doses.

The reduction factors to be used for the upper, central, and lower bound estimates for low-LET radiation are summarized in Table 2.4. In Table 2.5, these factors are applied to obtain estimates of risks for several cancer types resulting from chronic exposures at low dose rates. In Table 2.6, central estimates for exposures at several levels are presented.

Available epidemiological data are not adequate to obtain reliable estimates of the number of parameters required in a dose-response model that incorporates cell killing at higher doses, and most studies have not been analyzed in this manner. Thus we have not considered cell killing either in determining risk coefficients or in estimating effects for persons exposed to large doses (over 2 Gy [200 rad]).

2.3.2 Relative Versus Absolute Risk Projections

None of the populations on which estimates of health effects are based have yet been followed to the end of their life spans. This presents no problem for estimating the number of leukemia deaths since evidence from Japanese atomic bomb survivors indicates that leukemia rates return to spontaneous levels 25 or 30 years after exposure. In other epidemiological studies, bone cancer appears to follow the same pattern. Other cancers for which there is evidence of radiation induction, however, have minimal latent periods ranging from 10 to greater than 30 years, and the most recent data on Japanese survivors (Kato and Schull, 1982, and Wakabayashi *et al.*, 1983), extending the follow-up period from 1974 to 1978, indicate that the incidence of radiation-induced cancer is continuing to increase after 33 years of follow-up. Thus the use of a model in which risks are assumed to persist over an exposed individual's lifetime (the choice of BEIR III) now seems appropriate.

Two approaches are used in BEIR III to extend risk estimates beyond the period represented by follow-up data. With the absolute risk projection model, it is assumed that the number of excess cases per unit of population per unit of time expressed as a function of radiation dose remains constant over a specified time period. With the relative risk projection model it is assumed that the ratio of the excess cancer risk to the spontaneous age-specific risk remains constant over the specified period. After early childhood spontaneous cancer incidence and mortality rates generally increase with age, and because of this the relative risk model yields larger numbers for the years beyond the follow-up period.

The most recent data on Japanese survivors and the ankylosing spondylitis patients (Smith and Doll, 1983) indicate that risks increase as the population ages, and that the relative risk projection model may be more appropriate than the absolute model for most cancer sites. When absolute risks and relative risks for the Japanese survivors are examined by both age at exposure and age at death (see Table 2.7), relative risks are more constant over time for fixed age at exposure. In a parallel analysis of data from both Japanese survivors and British ankylosing spondylitis patients, Darby (1984) found that both studies were consistent with a model in which the relative risk was constant over time providing age at exposure was

Table 2.4 Reduction Factors for the Central and Lower Bound Estimates for Exposure to Low-LET Radiation

Dose, D	Reduction Factor[a]	
	Central Estimate	Lower Bound Estimate
For Dose Rates:		
< 0.05 Gy/day	0.30	0.10
≥ 0.05 Gy/day	0.30 + 0.47 D	0.10 + 0.60 D
For Total Doses, D(Gy) of		
0.01	0.30	0.10
0.10	0.35	0.16
0.25	0.42	0.25
0.50	0.54	0.40
0.75	0.65	0.55
1.00	0.77	0.70
1.25	0.89	0.85
≥ 1.50	1.00	1.00

[a] Formulae are appropriate for doses in Gy.

Table 2.5 Central Estimates (With Upper and Lower Bounds) For Lifetime Risks of Mortality Resulting From Low-LET Exposure Received at Low Dose Rates (< 0.05 Gy Per Day)

Effect	Number of Deaths (Per 10^4 Per Gy)			Years of Life Lost (Per 10^4 Per Gy)		
	Lower Bound[a]	Central Estimate[b,c]	Upper Bound[c,d]	Lower Bound[a]	Central Estimate[b,c]	Upper Bound[c,d]
Cancers Due to Other Than *In Utero* Exposure						
Leukemia	5	14	48	168	505	1682
Bone	0.2	1	2	7	22	75
Breast	4	60[e]	87[f]	97	955[e]	1452[f]
Lung	5	20	138[g]	100	288	1971[g]
Gastrointestinal	9	57	189	222	661	2202
Thyroid	0.7	2	7	20	61	203
Other	5	29	96	124	378	1260
Cancers Due to *In Utero* Exposure						
Leukemia	1.2[h]	1.2[h]	3	80[h]	80[h]	200
Other	1.2[h]	1.2[h]	3	80[h]	80[h]	200

[a] With the exception of cancers resulting from *in utero* exposure, these estimates are obtained by modifying the absolute linear estimates in Table 2.2 by the factor 0.10.

[b] With the exception of breast cancer and cancers resulting from *in utero* exposure, these estimates are obtained by modifying linear estimates in Table 2.2 by the factor 0.30.

[c] Central estimates and upper bounds for leukemia, bone, and thyroid cancer are based on the absolute risk model, while central estimates and upper bounds for remaining cancers are based on the relative risk model.

[d] These estimates are unmodified linear estimates.

[e] Non-age-at-exposure-specific linear estimate.

[f] Age-at-exposure-specific linear estimate.

[g] Based on a larger relative risk coefficient than the central estimate.

[h] These estimates are obtained by modifying the upper bound estimates by 0.4 (See Section 2.4.8).

Table 2.6 Central Estimates for Lifetime Risks of Mortality Resulting from Exposures to Several Doses[a]

	Number of Deaths Per 10^4 Population					Years of Life Lost Per 10^4 Population				
Dose (Gy)	0.01	0.10	0.50	1.0	2.0	0.01	0.10	0.50	1.0	2.0
Reduction Factor	0.30	0.35	0.54	0.77	1.00	0.30	0.35	0.54	0.77	1.00
Cancers Due to Other Than *In Utero* Exposure										
Leukemia	0.1	1.2	9.1	26	68	3.5	41	318	906	2354
Bone	0.006	0.07	0.6	1.7	4.3	0.2	2.6	20	58	150
Breast	0.6	6.0	30	60	120	9.5	95	477	955	1909
Lung	0.2	2.3	18	52	134	2.9	34	259	739	1918
Gastrointestinal	0.6	6.6	51	146	378	6.6	77	594	1695	4404
Thyroid	0.02	0.3	1.9	5.5	14	0.6	7.1	55	156	405
Other	0.3	3.4	26	74	192	3.8	47	340	970	2520
Cancers Due to *In Utero* Exposure										
Leukemia	0.01	0.1	0.6	1.2	2.4	0.8	8	40	80	160
Other	0.01	0.1	0.6	1.2	2.4	0.8	8	40	80	160

[a]With the exception of breast cancer and cancers resulting from *in utero* exposures these estimates are obtained by modifying linear estimates presented in Table 2.2 by the reduction factors in Table 2.4.

Table 2.7.1 Relative Risk For All Cancers Except Leukemia By Age ATB[a], 1.00+ Gy vs 0 Gy, 1950-1978 (Kato and Schull (1982) Table IV)

	Age at death					
Age ATB	*<30*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*
<10	15.1	5.0	6.8	—	—	—
10-19	1.0	2.5	2.4	8.2	—	—
20-34	—	1.8	1.9	2.0	1.6	—
35-49	—	—	1.2	1.1	1.3	1.4
50+	—	—	—	2.2	1.0	1.4

Table 2.7.2 Absolute Risk By Age ATB[a] (Excess Deaths/10^4 PY/Gy, 1950-1978) (Kato and Schull (1982) Table V)

	Age at death					
Age ATB	*<30*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*
			All cancer except leukemia			
<10	1.22	4.35	13.41	—	—	—
10-19	(0.03)	1.72	4.62	20.69	—	—
20-34	—	(1.35)	1.01	7.97	10.25	—
35-49	—	—	(0.26)	−0.96	2.09	12.67
50+	—	—	—	(17.39)	(0.53)	18.31
			Stomach cancer			
<10	0.18	0.40	13.84	—	—	—
10-19	(−0.11)	0.57	0.47	5.05	—	—
20-34	—	(0.10)	1.31	2.06	1.97	—
35-49	—	—	(1.61)	−1.20	−0.08	6.15
50+	—	—	—	(5.06)	(−1.39)	8.82
			Breast cancer			
<10	—	−0.02	—	—	—	—
10-19	—	0.80	1.16	—	—	—
20-34	—	(0.17)	−0.18	2.27	4.79	—
35-49	—	—	(−0.66)	−0.08	−0.10	−0.34
50+	—	—	—	(4.66)	(−0.17)	0.38
			Lung cancer			
<10	—	−0.01	−0.45	—	—	—
10-19	—	−0.02	0.96	7.48	—	—
20-34	—	—	−0.23	1.73	3.34	—
35-49	—	—	(−0.14)	0.59	1.19	4.72
50+	—	—	—	(−0.13)	(1.84)	0.29

[a] ATB = at the time of the bombing, 1945.

[b] Value of the highest age ATB of attained age class.

taken into account. By contrast, excess (or absolute) risks showed increasing trends with increased time from exposure.

Even though there is evidence that the absolute risk of radiation-induced cancer increases as a population ages, the increase observed thus far may not persist for a lifetime. Thus it is possible that the relative risk model will overestimate lifetime risks to some degree. We have nevertheless used the relative risk model for the central and upper bound estimates for most cancer sites (leukemia, bone, thyroid, and skin cancer are exceptions), but have also presented estimates based upon the absolute model. The latter are used for lower bounds.

The age distribution of the excess deaths will differ for the relative and absolute risk models with the relative risk model resulting in a higher proportion of cancer deaths at older ages. Thus, the ratio of estimates of years of life lost based on relative and absolute models will generally be lower than the analogous ratio of estimates of the numbers of deaths. At present, the absolute and relative risk projection models lead to very similar estimates of the number of years of life lost for most cancer sites (Table 2.2).

In addition to extrapolating beyond the period for which follow-up data are available, it is also necessary to extrapolate from the study population (Japanese survivors, ankylosing spondylitis patients, etc.) to the population for which risks are being estimated (U.S.). If a relative risk model is used for this purpose, then risks would be expressed as a proportional increase in spontaneous risks in the study population, and this proportional increase would then be applied to the spontaneous risks for the U.S. If, on the other hand, an absolute model is used, risks would first be expressed as absolute risks for the population studied, and then expressed as a proportional increase in the spontaneous cancers expected to occur in the U.S. during the follow-up period on which the estimates were based. This proportional increase or relative risk would then be used to extrapolate beyond the follow-up period. For risk estimates obtained from the Japanese studies, these two procedures can differ markedly since spontaneous rates differ substantially in the two countries for some cancer sites, such as lung, breast, and stomach (American Cancer Society, 1978).

Even though there is considerable evidence to indicate that excess cancer risks depend upon age and probably other variables, it is not clear that such risks depend upon all factors affecting spontaneous risks. If, for example, radiation-induced cancers are predominantly of certain pathological types, it is probably not appropriate to extrapolate relative risks from one population to another if the distribution of types differs. Data on radiation-induced breast cancer in Japanese and North American populations suggest that estimates expressed as absolute risks are more comparable across populations than estimates expressed as relative risks (Land *et al.*, 1980). Unfortunately, for other cancer sites, data on Caucasian populations are limited.

In BEIR III, the absolute risk model was used for extrapolating across populations, and, in determining relative risk estimates for most cancer sites. We have also used this approach. However, relative risks estimated directly from the study populations are considered and discussed in Section 2.4.

If radiation-induced risks were proportional to risks from all other factors (relative risk model), then risk estimates would depend on spontaneous cancer rates for geographical locations where nuclear power plants are located. This would suggest the use of local rather than national rates for calculating lifetime risks based on the relative risk model. However, in the absence of knowledge as to whether or not all factors contributing to geographic variability in

cancer rates also affect risks of radiation-induced cancers, this approach does not seem justified. Local cancer rates are frequently less reliable and more difficult to obtain than national rates. It is unusual for local cancer rates to differ from the national average by more than a factor of two or three, and the largest differences tend to be instances in which rates for relatively low population areas are much lower than the national average (Mason *et al.*, 1975).

2.3.3 Incidence Versus Mortality

Risk estimates for lung cancer, gastrointestinal cancers, and the residual group of "other" cancers are based primarily on mortality data, and thus require adjustment to obtain incidence estimates. This is done by assuming that the relative risk coefficients (expressed as a percent increase per Gy) are the same for incidence and mortality. The relative risk coefficients can then be applied to U.S. incidence rates to yield lifetime relative risk incidence estimates. To obtain absolute risk estimates, the ratio of the lifetime relative incidence and mortality estimates is multiplied by the lifetime absolute risk estimate for mortality (see Section 2.5 for an example).

For breast cancer and thyroid cancer, the risk coefficients are based primarily on incidence data, and thus must be adjusted to obtain mortality estimates. For breast cancer, the relative risk coefficients are applied to U.S. mortality rates to obtain a mortality estimate, and to U.S. incidence rates to obtain an incidence estimate. To obtain an absolute mortality estimate, the ratio of these two estimates is multiplied by the absolute incidence estimate. For thyroid cancer, the relative risk projection model is not used, and mortality estimates are obtained by multiplying incidence estimates by 0.10 as discussed in Section 2.4.6.

Estimates for leukemia and for all cancers resulting from *in utero* exposure are based on data collected at a time when mortality from these cancers was very nearly 100%. Cure rates for leukemia and for other childhood cancers have improved substantially in recent years. The average five-year survival rate for leukemia for the period 1973-1980 was 32%, and that for all childhood cancers (including leukemia) is 57% (National Cancer Institute, 1984). The survival rates vary by the type of leukemia and by the age at diagnosis. These improving cure rates have not been incorporated into our model, and thus estimates of mortality from leukemia and other childhood cancers are probably somewhat high. A rough correction would be to reduce these mortality estimates by utilizing the cure rates given above. This correction would not, however, take account of the fact that some types of leukemia are more readily induced by radiation than others (and may differ with respect to cure rate), and that a five-year survival rate cannot necessarily be considered a cure rate.

Cure rates for cancers other than leukemia are also improving (National Cancer Institute, 1984). It is thus possible that mortality resulting from future cases is overestimated by the model used in this report.

The occurrence of cancer can be expected to reduce the quality of life after the time of occurrence. The extent of the reduction of quality is difficult to quantify and will vary considerably depending on many factors such as cancer site, the course of the disease, and various psychological factors. An attempt to measure the impact of cancer (other than death) has been made by estimating the number of years of life after cancer occurs per 10^4 population per Gy (Table 2.3).

2.3.4 Latent Period

The procedure commonly used to account for a latent period (BEIR I; BEIR III; UNSCEAR 77; Reactor Safety Study, 1975) is to assume that there is no risk of radiation-induced cancer for some specified period following exposure and that this is followed by a period of constant risk (either absolute or relative). This procedure represents a simplification as the actual distribution over time probably shows a build-up and possibly eventually a tapering off of effects. For leukemia, the minimal latent period is about 2-3 years and the excess shows a peak about 5-10 years after exposure and then gradually tapers off. For most cancer sites, however, the distribution of cancer deaths over time is not yet known, although the Japanese data indicate that after 34 years absolute risks are continuing to increase (except for leukemia).

For some cancer sites, the latent period appears to be related to age at exposure. With a relative risk model, however, those exposed at younger ages may exhibit long latent periods because they must pass through several years with very low spontaneous risks. A small percent increase in these very low rates is not likely to be statistically detectable.

Latent periods for incidence and mortality will differ. Due to the general uncertainty in estimating distributions over time, our risk projection model does not reflect such differences. However, substantial spontaneous risk will often begin earlier in life for incidence than for mortality. Thus, for those exposed early in life, the relative risk model will tend to provide different latent periods for incidence and mortality.

For the calculations in this report, the minimal latent period is taken to be two years for leukemia and bone cancer, five years for thyroid cancer, and ten years for other cancer sites, choices that are supported by epidemiological data (BEIR III). In addition to the minimal ten-year latent period, it is assumed that radiation-induced breast cancer does not occur until age 30 and that radiation-induced lung cancer does not occur until age 40. This additional assumption is based on the experience of the Japanese atomic bomb survivors, and provides a longer latent period for those exposed early in life. This assumption has almost no effect on estimates based on the relative risk projection model, but does affect estimates based on the absolute risk projection model.

2.3.5 Age at Exposure

Data from epidemiological studies indicate that radiation risks depend upon age at exposure. As can be seen from Table 2.7 (Kato and Schull, 1982), both absolute and relative risks decrease with age at exposure when age at death is held fixed. Analyses by Darby (1984) clearly demonstrate a decrease in relative risk with increasing age at exposure among Japanese survivors. Although no significant decrease with age at exposure was demonstrated among ankylosing spondylitis patients in the Darby analyses, data on this population were not inconsistent with the result demonstrated for the Japanese survivors.

Especially large relative risks have been demonstrated in the youngest age groups, and it is the extrapolation of these large relative risks over a lifetime for those who are young at exposure that accounts for much of the difference in the relative and absolute risk projections given in BEIR I and BEIR III. In BEIR III this effect was mitigated somewhat by substituting relative risk estimates based on those who were 10-19 at exposure for the under 10 age at exposure group.

Although it would be desirable to take age at exposure into account in estimating lifetime risks, the estimates of the relative risk coefficients for those under age 20 at exposure are based on a fairly small number of cancer deaths that have occurred in this group. These estimates have very large variances, especially for the site-specific estimates required for this report. It is, of course, this age-at-exposure group for which the greatest projection of risks is required, and it does not seem desirable to use very imprecise estimates for the projection.

Therefore, data from all age-at-exposure groups have been pooled to estimate the relative risk coefficients for most cancer sites. The procedure used to do this is described in Section 2.6. This can be regarded as a compromise measure and does not reflect a belief that age at exposure is not important. Even if the age-at-exposure-specific relative risk coefficients could be estimated reliably, it is not known whether such risks will continue to be expressed late in life decades after the exposure has occurred and when spontaneous risks are very much larger. Even without the use of age-at-exposure-specific estimates, it is very possible that a lifetime relative risk model overestimates risks (see Section 2.3.2).

Thus, for most cancer sites, a single relative risk estimate based on combined data from all exposure ages has been used to calculate the central and upper bound risk estimates. This approach generally yields a lifetime risk that is intermediate between the relative and absolute risk projections based on age-at-exposure-specific estimates. Exceptions to this approach are thyroid cancer and the upper bound for breast cancer for which the evidence for increased risks for those exposed early in life (under age 20) is especially strong, as discussed in Sections 2.4.3 and 2.4.6. Eventually it is hoped that additional data, and analyses that provide models for the effect of age at exposure will permit taking the effect of age at exposure into account without sacrificing the precision of the lifetime risk estimates.

2.4 Determination of Risk Estimates for Several Cancer Sites

In the Reactor Safety Study (1975), estimates for various cancers were obtained (with some modification) from the BEIR I report. In determining site-specific estimates for this report, we have relied primarily upon the following sources:

1) Appendix A of BEIR III where available data on each cancer site are discussed in detail.
2) The most recent analyses of mortality data from the Japanese Life Span Study (Kato and Schull, 1982) and of incidence data from the Nagasaki Tumor Registry (Wakabayashi *et al.*, 1983) which have been updated to include an additional four years (1975-1978) of follow-up data since the publication of BEIR III.
3) The most recent report (Smith and Doll, 1982) on risk estimates in ankylosing spondylitis patients treated with radiation.

The absolute and relative annual risk coefficients used in calculating lifetime risks are indicated in Tables 2.2 and 2.3 and are discussed below. With the exception of breast cancer, relative risk estimates are obtained by expressing the number of deaths expected based on applying the absolute risk coefficients to the 10th through 33rd year of follow-up as a fraction of the spontaneous deaths expected during this period (see Section 2.6). The procedure is similar to that used in BEIR III except that the follow-up period has been extended by four years to account for the fact that the most recent data from the Japanese studies are included.

Lifetime risk estimates for mortality as well as years of life lost based on the relative and absolute risk models are also presented in Table 2.2. Analogous estimates for incidence are presented in Table 2.3. These are upper bound linear risk estimates that must be modified as indicated in Section 2.3.3 to obtain linear-quadratic and low-dose-rate risk estimates that are used as central and lower bound estimates for most cancer types. The lifetime risks are calculated using a life table based procedure similar to that used in BEIR III. A detailed description of the computational procedure is given in Section 2.6.

2.4.1 Leukemia

For leukemia, we have used the risk estimate of 2.24 deaths per 10^4 PY per Gy given in BEIR III and based on analysis of Leukemia Registry data for Japanese atomic bomb survivors. This estimate is very close to the linear estimate of 2.0 deaths per 10^4 PY per Gy obtained from ankylosing spondylitis patients once cell killing is taken into account (Smith and Doll, 1982). The estimate is assumed to apply 2-27 years after exposure.

For the purpose of estimating the total number of leukemia cases, there is no need to choose between the absolute and relative risk models. For the purpose of estimating years of life lost, however, the distribution of these deaths over time must be taken into account. Since spontaneous rates for leukemia increase with age (except for a peak early in life), the choice of the absolute or relative risk model will affect the estimation of this distribution. After reaching a peak between 5 and 10 years after exposure, the rates for radiation-induced cases decrease to zero between 25 and 30 years after exposure. Neither the absolute nor the relative risk model applied over the total life span conforms to this distribution. The model used here employs a minimal latent period of 2 years and a plateau period of constant absolute risk from 2 to 27 years. Within the plateau period the use of a relative risk model would result in a monotonic increase in absolute risk, initially lower than the estimates obtained in the absolute risk model and ultimately higher. This gives a slightly better fit to the radiation-induced excess in the first part of the period but a poor fit at the end of the period. A more complex model with a rise and fall within the period would fit better the current overall leukemia data of the Japanese study. However, such a model is not necessarily preferable since the precise shape of the time-incidence curve varies with both age at exposure and histologic type of leukemia, and no single model could fit all groups.

The upper bound lifetime risk estimate for leukemia is 48 deaths per 10^4 per Gy, which represents 1656 years of life lost per 10^4 per Gy. These estimates are based on a life table approach that accounts for the fact that some exposed persons will die for reasons unrelated to radiation exposure before 27 years have passed (see Section 2.6). The use of the age- and gender-specific estimates (as in BEIR III) yields similar risk estimates.

2.4.2 Bone Cancer

For bone cancer, we have used a risk estimate of 0.1 deaths per 10^4 PY per Gy, assumed to apply 2-27 years following irradiation. The risk estimate of 0.05 deaths per 10^4 PY per Gy for bone cancer given in BEIR III, was obtained mainly from data on patients given injections of radium-224. It was derived from an estimate of 1.0 deaths per PY per Gy alpha on the assumption that 20 is an appropriate RBE for alpha particles. The expression period was assumed to be similar to leukemia. Material in UNSCEAR 77, however, indicates that a lower

RBE may be somewhat more consistent with limited data on exposure to low-LET radiation. Lifetime risks of 2-5 deaths per 10^4 per Gy are suggested, which would correspond to annual risks of 0.08-0.20 deaths per 10^4 PY per Sv if a 25-year expression period is assumed.

2.4.3 Breast Cancer

Our estimates for female breast cancer are based on those given in BEIR III which were obtained from incidence data from a New York study of women treated with x-rays for acute postpartum mastitis and from a Massachusetts study of women given fluoroscopic examinations of the chest. (See Boice *et al.*, 1979, for a review of these studies.) The absolute risk estimates are 10.4 cases per 10^4 woman year (WY) per Gy for women aged 10-19 years at exposure and 6.6 cases per 10^4 WY per Gy for women aged $\geq$20 years at exposure, while the respective relative risk estimates for these two groups are 103% per Gy and 42% per Gy. These estimates are based on the assumption of a latent period of 20 years for women aged 10-14 at exposure, of 15 years for women aged 15-19 at exposure, and 10 years for women aged $\geq$20 at exposure.

Age-at-exposure-specific risk estimates for the Japanese atomic bomb survivors (Land *et al.*, 1980) for the two populations noted above suggest that absolute risk coefficient estimates are fairly comparable across populations, but that relative risk coefficient estimates are larger for the Japanese women. The risk of naturally occurring breast cancer is much lower in Japan than in the United States. BEIR III breast cancer estimates were based on the U.S. data and we have followed the same procedure.

Very few women in the U.S. studies were over 40 years of age at exposure. The Japanese data show no evidence of radiation-induced breast cancer in women between 40 and 49 years of age at exposure, but there is evidence of a radiation effect for women exposed at ages over 50. The most recent Japanese data indicate that females exposed under age 10 are showing an excess of breast cancer (Tokunaga *et al.*, 1982). Since the risk estimates for those aged 10-19 at exposure have very large standard deviations (3.8 for the absolute risk estimate and 0.64 for the relative risk estimate), for the central estimate, we have pooled the estimates for the 10-19 and the $\geq$20 years-of-age groups (weighting by their inverse variances). This results in an absolute risk coefficient estimate of 7.4 cases per 10^4 WY per Gy and a relative risk coefficient estimate of 45% per Gy. These estimates are applied to all age-at-exposure groups including those under 10 years as well as those over 40 years of age. For the upper bound, an age-specific risk projection has been used by applying the estimates for those 10-19 years of age at exposure for all who were under 20 years of age at exposure, and the estimate for women aged 20 and over for all others.

With both approaches, risks are assumed to begin at age 30 or after a minimal latent period of 10 years, whichever occurs later. The linear model is used for both the upper bound and the central estimate of breast cancer risk since there is little evidence that reduction in dose or dose rate will reduce risks. However, the two estimates differ with regard to the treatment of age at exposure as described in the previous paragraph. These procedures are summarized in Table 2.1, and lifetime incidence estimates based on the procedures described above, using both relative and absolute projection models, are presented in Table 2.3. Mortality estimates, which are presented in Table 2.2, are obtained as described in Section 2.3.3 and in Section 2.6.

2.4.4 Lung Cancer

Because a portion of the exposure received in a nuclear power plant accident will result from inhalation of radioactive material, lung cancer may account for a high proportion of the total cancer deaths resulting from such an accident. Unfortunately, none of the available estimates of lung cancer risks are completely applicable to the situation of interest in this report. Estimates from studies of uranium miners are based on high-LET rather than low-LET exposure, while estimates based on the Japanese data may not be entirely appropriate since naturally occurring lung cancer is much lower in Japan than in the United States. Estimates based on British ankylosing spondylitis patients are derived from a diseased population for whom individual dose estimates are not available.

The estimates obtained from the studies including low-LET exposure are presented in Table 2.8. For the Japanese studies, estimates based on total kerma (as presented in the source papers) as well as estimates based on the dose equivalent to the lung (Sv) are presented. The latter utilize the ratios of organ and kerma doses with an RBE of 10 as provided by Kerr (1979) and presented in BEIR III. For lung, this ratio is 0.90 for Hiroshima, 0.53 for Nagasaki, and 0.75 for the combined cities. Relative risks are also presented. These were obtained by expressing the estimated number of radiation-induced deaths (Table 8, Kato and Schull, 1982; and Table VI, Wakabayashi *et al.*, 1983) as a percent of the spontaneous deaths and dividing by the average dose, again correcting so that estimates are expressed according to the dose equivalent to the lung (Sv) assuming an RBE of 10.

The Japanese data provide no evidence that radiation-induced lung cancer occurs before the age of 40. Thus it is assumed that there is no risk up to this age or until a 10 year minimal latent period has passed. The fact that the estimates based on the Japanese data include person-years before this age and, in the case of mortality data, before the minimal 10 year latent period, means that absolute risk estimates should be adjusted upward. The Supplementary Tables from Kato and Schull (1982) do not provide data by age at risk, but a risk estimate based on data from 1955-78 for those exposed at age 20 and over and on data from 1971-78 for those exposed at age 10-19 has been calculated and should approximate the desired estimate based on person-years after age 40. This estimate is 1.66 deaths per 10^4 PY per Sv.

Lung cancer has been under-reported on death certificates in Japan (Steer *et al.*, 1976). This provides another reason for adjusting upward the absolute risk estimates from the Life Span Study. We have used an absolute risk coefficient estimate of 2.0 deaths per 10^4 PY per Gy to be applied only after age 40 or after a minimal 10 year latent period has passed.

When absolute risks for lung cancer are examined by age at exposure and age at death (Table 2.7), absolute risks increase with time for fixed age at exposure, thus supporting the use of the relative risk model for projecting beyond the follow-up period. If it is assumed that the absolute risk coefficient of 2.0 deaths per 10^4 PY per Gy is applicable to the U.S. population, then this estimate can be obtained by expressing the number of radiation-induced deaths that would occur in the U.S. population over a period 10-33 years following exposure as a percentage of the spontaneous deaths that would occur during the same time period. This approach yields an estimate of 18% per Gy, about half the relative risk coefficient of 37% obtained directly from the Japanese data. (The various biases discussed above should not affect relative risk estimates provided they are not related to exposure). The discrepancy between the two estimates results from the fact that U.S. lung cancer rates are more than

Table 2.8 Absolute and Relative Risk Estimates for Lung Cancer. (Standard errors are given in parentheses).

Study	Risk Estimate		
	Absolute-based on total air kerma (deaths per 10^4 PY per Gy)	Absolute-based on dose to the lung[d] (deaths per 10^4 PY per Sv)	Relative-based on dose to the lung[d] (% per Sv)
Japanese Life Span Study[a]			
Hiroshima	0.83 (0.20)	0.92 (0.22)	41 (11)
Nagasaki	0.34 (0.23)	0.64 (0.43)	31 (21)
Both Cities	0.61 (0.15)	0.81 (0.20)	37 (10)
Nagasaki Tumor Registry[b]	0.87 (0.37)	1.64 (0.69)	49 (23)
Ankylosing spondylitis patients[c]	-	2.55 (0.85)	25 (9)

[a] Kato and Schull (1983)

[b] Wakabayashi et al. (1983)

[c] Smith and Doll (1982)

[d] An RBE of 10 is assumed. See text for complete explanation.

double those in Japan.

Although the value 18% is somewhat closer to that obtained from the British ankylosing spondylitis patients (25%), and although the comparison of breast cancer risks in Japan and the U.S. discussed in Section 2.4.3 would also support the use of this value (18%), there is still considerable uncertainty as to which choice is more appropriate. Since presumably the lower spontaneous lung cancer risks for the Japanese are due, at least in part, to a lower frequency of smoking, one way to address this question is to examine the interaction of smoking and radiation. An additive model would suggest that the value of the risk coefficient based on U.S. spontaneous rates (18%) is more appropriate, while a multiplicative model would support using the value of 37% based on Japanese spontaneous rates. Unfortunately, results of an analysis of the interaction of risks from smoking and radiation among Japanese atomic bomb survivors (Prentice, 1983) are equivocal. Although an additive model fit the data somewhat better than a multiplicative one, the data were not adequate to rule out either choice. However, in a recent analysis by Whittemore (1983) of data on radon decay product exposure and smoking in U.S. uranium miners, the multiplicative model provided a significantly better fit than did the additive model.

The coefficient 18% has been used for the central estimate, and the coefficient 37% has been used for the upper bound. The absolute risk projection model is used to obtain the lower bound. The linear mortality estimates based on these models are presented in Table 2.2. For comparison, the lifetime risk estimate based on the BEIR III coefficients has been calculated and is 121 deaths per 10^4 per Gy. This value is larger than the linear relative risk estimate based on the coefficient of 18% (67 deaths per 10^4 per Gy), but slightly smaller than the upper bound estimate based on 37% (138 deaths per 10^4 per Gy).

In this report, estimates are based primarily on data from the Japanese atomic bomb survivors rather than on miners exposed to radon decay products. This is done partly to avoid the need to extrapolate from high-LET to low-LET exposure, and partly because data from many of the mining populations studied has not been analyzed in a way that examines both age at exposure and age during the follow-up period in sufficient detail. Estimates of the relative risk coefficient based on mining populations range from 1.8% per WLM (working level month), calculated from data on Czechoslovakian miners (BEIR III), to 0.31% (Whittemore, 1983) based on an analysis of U.S. miners in which smoking was taken into account. In BEIR III, it is indicated that the conversion factor to obtain rad from WLM is in the range of 0.4 to 0.8 (1 WLM = 0.004-0.008 Gy) while the RBE for alpha irradiation is in the range of 8 to 15. The conversion factor used in BEIR III to convert risks based on WLM to risks based on rem was approximately 7. If it is assumed that 1 WLM = 0.07 Sv, the estimates above (of 1.8% and 0.31% per WLM) correspond to 26% per Sv and 4% per Sv respectively. These estimates are reasonably comparable with those based directly on low-LET exposure.

2.4.5 Gastrointestinal Cancers

Evidence that most cancers of the gastrointestinal tract including the pancreas can be radiation-induced is found mainly in the two Japanese studies and in the study of ankylosing spondylitis patients. The evidence for radiation-induced gastrointestinal cancer including estimates obtained from various studies has been summarized by Land (1983). These estimates are presented in Table 2.9. There is considerable uncertainty in the estimates, and it is difficult to reconcile the discrepancy between the Japanese Life Span Study and the Nagasaki

Table 2.9 Risk Estimates for Mortality from Cancers of the Gastrointestinal Tract (deaths per 10^4 PY Gy)[a] (Standard errors are given in parentheses).

Site	Study		
	Japanese Life Span Study	Nagasaki Tumor Registry[b]	Ankylosing Spondylitis Patients
Esophagus	0.21 (0.24)	-	0.25 (0.16)
Stomach	1.04 (0.30)	2.36 (1.07)	2.11[f] (1.08)
Colon	0.46 (0.13)	0.51 (0.31)	1.70 (1.21)
Rectum	-	0.47 (0.28)	-
Pancreas	-	1.04 (0.83)	0.70 (0.61)
Other and unspecified	0.53 (0.17)	0.70[d] (0.52)	
TOTAL	1.80[c] (0.45)	5.08[e]	

[a] Estimates are those given in Land (1983). All estimates are given in terms of organ dose with Japanese estimates based on an RBE of 11.3 for neutron exposure.

[b] These estimates (and their standard errors) are adjusted by multiplying by mortality-incidence ratios taken to be 0.77 for the stomach, 0.5 for the intestine (colon and rectum), 0.90 for pancrease, 1.0 for liver.

[c] Since the Life Span Study estimates for rectum and pancreas would be negative, this total is less than the sum of the estimates presented.

[d] This estimate is for liver cancer only.

[e] This estimate is obtained by summing the individual sites. It probably overestimates the true total since estimates for sites not given would be negative.

[f] Alternative estimates of dose to the stomach yield estimates of 2.81 (1.43) and 0.75 (1.21).

Tumor Registry. The standard errors for the estimates obtained from the Tumor Registry and from the study of ankylosing spondylitis patients are considerably larger than those obtained from the Japanese Life Span Study. The Life Span Study has less potential for bias than does the Registry where cases are not likely to be obtained for survivors who have migrated, and for this reason it seems important to choose estimates that are reasonably consistent with the Life Span Study.

Estimates for mortality from cancers of the esophagus, stomach, colon, and other and unspecified gastrointestinal cancers were obtained by weighting the estimates presented in Table 2.9 by their inverse variances. Since estimates for mortality from cancers of the pancreas and rectum based on the Life Span Study would be negative, and since these estimates and their standard errors are not presented by Land (1983) or by Kato and Schull (1982), obtaining estimates for these sites required a more subjective weighing of evidence from the three studies. The resulting mortality estimates are as follows:

Site	**Excess Cancer Mortality** (Deaths per 10^4 PY per Gy)
Esophagus	0.2
Stomach	1.2
Colon	0.5
Rectum	0.1
Pancreas	0.2
Other GI	0.5
All	2.7

The total estimate of 2.7 deaths per 10^4 PY per Gy marks the upper 95% confidence limit for the Life Span Study. The estimates above do not differ greatly from those presented in BEIR III (Table V-14, p. 198).

There are a number of uncertainties in the above estimates. Death rates for stomach cancer are about eight times higher in Japan than in the United States (American Cancer Society, 1978), a fact that could inflate the absolute risk coefficients obtained from the Japanese studies. For the ankylosing spondylitis patients, estimates of the radiation dose to the stomach ranges from 0.67 to 2.5 Gy resulting in a range of estimates of 0.8-2.8 deaths per 10^4 PY per Gy. Finally, data on cervical cancer patients provide no evidence of an

association of radiation and stomach cancer although Land (1983) has noted that these data are not inconsistent with estimates from other studies. The pancreas data fail to show an association with radiation in the Life Span Study, possibly because death certificate diagnosis for this cancer is poor. For both the Nagasaki Tumor Registry and the ankylosing spondylitis patients, the confidence intervals for this site include zero. The value of 0.5 deaths per 10^4 PY per Gy given for other gastrointestinal cancers may be an underestimate; in BEIR III, the estimate for liver cancer alone is 0.7 deaths per 10^4 PY per Gy, obtained from patients given thorotrast injections. For salivary gland tumors, Land (1983) obtained an estimate of 0.25 deaths per 10^4 PY per Gy based on several studies, mostly of patients irradiated to the head and neck during infancy and childhood.

The absolute risk estimates for gastrointestinal cancers based on the Japanese Life Span Study presented by Land (1983) show a distinct increase with age at exposure. This fact, together with the sharp increase in risks obtained from the most recent Japanese data (1975-1978), provides support for the relative risk model. In the analysis of Darby (1984), cited earlier as providing support for the relative risk model, well over half the cancers in the group analyzed for the Japanese survivors were gastrointestinal cancers. Relative risks for gastrointestinal cancers decrease with age at exposure, but Land (1983) notes that this decrease is only of borderline statistical significance.

The relative risk estimate obtained by expressing the number of radiation-induced deaths expected 10-33 years following exposure as a fraction of the spontaneous deaths expected in the U.S. population in this period is 39% per Gy. This value is considerably larger than the relative risk of 12% per Gy (Land, 1983), based on the Life Span Study, and slightly larger than the relative risk of 33% per Gy, which can be calculated from data from the Nagasaki Tumor Registry (Wakabayashi *et al.*, 1983). Japanese and American spontaneous rates for stomach cancer, the largest contributor to radiation-induced gastrointestinal cancers, differ substantially. We have used an estimate of 39% per Gy. Lifetime risk estimates based on the linear model are presented in Tables 2.2 and 2.3.

2.4.6 Thyroid Cancer and Benign Thyroid Nodules

The linear risk coefficients for thyroid cancer and for benign thyroid nodules are those presented in Volume II Appendix A, where data from several epidemiological studies of thyroid effects are reviewed. These linear coefficients are used to provide upper, central, and lower estimates.

In Volume II Appendix A, the Thyroid Effects Committee concludes that, based on human experience, ^{131}I is no more than one-third as carcinogenic to the thyroid gland as external x-irradiation. However, the human data are considered insufficient to permit meaningful calculations of the lower, central, and upper bound estimates required for the purposes of this report. Therefore, data from animal studies have been used to meet these requirements until more human data become available. Based on animal data, the risk estimates for external radiation are multipled by 1/10 (lower bound), 1/3 (central bound), or 1/1 (upper bound) to give risk estimates for exposure to ^{131}I. For benign thyroid nodules, the central and lower bound estimates for ^{131}I are taken to be one-fifth of those for external radiation with an upper bound estimate of 1:1. The choice of the value one-fifth is discussed in Appendix A. For the upper bound for the risk of both thyroid cancer and benign nodules, ^{131}I is assumed to

be equally as effective as external beam irradiation.

An absolute risk model is used to determine lifetime risks for thyroid cancer. Data on thyroid effects are mainly from populations who were very young at exposure, and whose follow-up periods include years when spontaneous risks are very low. This makes it very difficult to estimate relative risk coefficients reliably. Furthermore, spontaneous rates for thyroid cancer show very little increase with age after about age 30. Thus, differences in lifetime risks based on relative and absolute risk projection models do not differ as much as for other cancers (see Appendix A.A).

Although data on populations exposed at older ages are limited, risks of thyroid effects appear to be much smaller for those who are older at exposure; in fact, there is very little evidence of radiation-induced thyroid effects for those exposed over 30 years of age. The age-at-exposure-specific coefficients given in Tables 2.2 and 2.3 and discussed in Appendix A are used for calculating thyroid risks. Risks of thyroid effects are greater for females than for males. In general, the use of gender-specific coefficients is recommended. However, provided the exposed population is approximately equally divided between the genders, then the effects of gender-related differences on the total population risk would not be large.

It is estimated that approximately 10% of thyroid cancers will prove fatal (Appendix A). To obtain mortality estimates, incidence estimates are multiplied by 0.10. It is recognized that the distribution over time is different for mortality and incidence, with deaths tending to occur later in life (see Appendix A.B). This results because cure rates vary by age of occurrence, and because there is sometimes an interval of several years between the occurrence of cancer and death. Differences in timing are not accounted for in our model, so that years of life lost due to thyroid cancer are probably overestimated. Since thyroid cancer makes a relatively small contribution to the total number of cancer deaths resulting from a nuclear power plant accident (see Table 2.2), this overestimation does not represent a serious problem.

2.4.7 Skin Cancer

Skin cancer is not as serious a health problem as cancers of other types, and is unlikely to be a significant contributor to the total deaths resulting from a power plant accident. The BEIR III Committee did not include skin cancer in its risk estimates for cancer mortality and incidence. However, beta emitters deposited on the skin in a nuclear power plant accident could result in doses to the skin that are far greater than to other parts of the body. Thus, risks of radiation-induced skin cancer are estimated in this report even though quantification of such risks is difficult in view of the limited data available.

The risk of radiogenic skin cancer resulting from exposure in a nuclear power plant accident is especially difficult to assess for a number of reasons. First, because skin cancer is a much less serious disease than most other cancers, it cannot be adequately evaluated using Tumor Registry or mortality data. This may be one reason that some epidemiological studies have reported largely negative results. Second, there may be a potentiating effect of exposure to ultraviolet radiation leading to sensitivity that varies greatly by the part of the body exposed as well as by race. (Blacks and Japanese appear to have greatly reduced risks.) In a nuclear power plant accident, those areas of the body with the highest exposure from beta emitters would be those areas that are relatively unprotected by clothing and thus also exposed to the greatest amount of sunlight (and thus ultraviolet radiation). Third, those

studies that are suitable for risk estimation have involved partial-body irradiation; the appropriate manner of extrapolating to a situation in which the whole body is irradiated (to varying degress) is not known. Fourth, most studies have been based on x-irradiation which may have greater penetrating properties than beta emitters; again, the effect of this difference on skin cancer induction is uncertain. Finally, multiple radiation-induced skin cancers in the same person are not uncommon. In this report, we estimate only the number of people who will develop such cancers, not the total number of cancers.

The evidence regarding radiation-induced skin cancers has recently been reviewed by Albert and Shore (1984). Their report includes risk estimates from several studies including an estimate of 2.4 per 10^4 PY per Gy based on a study of persons treated as children by x-ray for ringworm of the scalp described by Shore *et al.* (1984), and an estimate of approximately 0.5 per 10^4 PY per Gy obtained from a thymus-irradiation study by Hempelmann *et al.* (1975). Several other studies, however, have shown little or no evidence of radiation-induced skin cancer, but in most instances these studies were either based on data where under-reporting may have been a problem, involved exposure to parts of the body where skin cancer may not be as likely to occur, or, in the case of the Japanese A-bomb survivors, involved a population with very low spontaneous rates. Available data on skin cancer risks are not adequate to determine the shape of the dose-response function, latency, or the effect of age at exposure, but the limited evidence available is consistent with findings for most other cancers. Shore *et al.* (1984) found that the relative risk model fit the temporal pattern of radiation-induced skin cancer better than the absolute risk model.

For the linear upper estimate, we have used 2.0 per 10^4 PY per Gy. This estimate is on the high side but, as noted above, many of the studies may have suffered from under-reporting, while the Japanese study may not be applicable to assessing risks for the U.S. population. Risk calculations are to be made on the basis of the dose to the face since about 85% of basal cell carcinomas (the predominant type resulting from radiation exposure) occur on the head and neck (Koph, 1979); additional exposure to other parts of the body has not been taken into account. Central and lower estimates have been modified by the reduction factors in Table 2.4. These factors do not, of course, modify estimates for exposure exceeding 1.5 Gy, which can be expected to be a more common occurrence for skin dose than for doses to other parts of the body. Risks due to very large doses, and the possibility of cell killing at such doses, cannot be adequately assessed from the available data; we have simply used linear estimates for such doses. Because of the difficulty in obtaining reliable and appropriate estimates of spontaneous risks, we have used the absolute risk model for calculating lifetime risks. A ten-year latent period has been assumed. These assumptions lead to a lifetime linear risk estimate of 67 cases per 10^4 per Gy. Because skin cancer, particularly basal cell carcinoma, is rarely fatal, we do not attempt to estimate skin cancer mortality.

2.4.8 Other Cancers

Other cancers for which there is reasonably good evidence of an association with radiation include lymphoma, multiple myeloma, and cancer of the urinary bladder and brain. Evidence of an association for cancers of the kidney, ovary, uterus, and cervix uteri is somewhat weaker. In addition to the cancers considered in the above sections, BEIR III presents site-specific incidence estimates of about 0.6 deaths per 10^4 PY per Gy for urinary cancer, 0.27 deaths per 10^4 PY per Gy for lymphoma, and a residual estimate of 1.0 deaths per 10^4 PY per

Gy. However, estimates based on Japanese survivors (Kato and Schull, 1982) suggest that these risks could be much smaller.

We have used an estimate of 1.5 deaths per 10^4 PY per Gy for all other cancers. In calculating relative risks for other cancers, spontaneous rates for all cancers are used with leukemia, bone, breast, lung and gastrointestinal cancers subtracted out. Rates for skin and prostate cancer were also subtracted, as was done in BEIR III. As with most other cancer types, a 10-year minimal latent period has been assumed. Data on these cancers is not adequate to investigate the adequacy of the relative risk model or the effect of age at exposure.

2.4.9 Cancers Resulting From in Utero *Exposure*

The estimates provided in BEIR III for the effect of *in utero* irradiation are obtained from the Oxford Survey of Childhood Cancer (Stewart and Kneale, 1968; Stewart *et al.*, 1958) of children of patients receiving x-ray pelvimetry. These estimates are 25 deaths per 10^4 PY per Gy for leukemia persisting for 12 years from birth, and 28 deaths per 10^4 PY per Gy for fatal cancers of other types and persisting for 10 years from birth. If it is assumed that for each 100 persons (males and females) there is one fetus *in utero*, these estimates yield lifetime population risks of about 3 cases each of leukemia and other fatal cancers per 10^4 per Gy. The life years lost would be a total of about 400 per 10^4 per Gy. Even though the contribution to the total population risk is small, it is important to note that the lifetime risk of leukemia for persons exposed *in utero* (300 deaths per 10^4 per Gy) is about six times that for persons exposed later in life (48 deaths per 10^4 per Gy).

Other studies of children x-rayed *in utero* have indicated somewhat smaller relative risks than those obtained in the Oxford study, but do not provide sufficient dose information to calculate risk per Gy (MacMahon, 1962; Graham *et al.*, 1966; Diamond *et al.*, 1973). Furthermore, no excess cancer deaths have been observed among those exposed *in utero* from the atomic bombs in Hiroshima and Nagasaki. Jablon and Kato (1970) estimated that 5.2 excess deaths should have occurred if risks were similar to those observed in the Oxford study.

It is likely that the values presented from the Oxford Survey overestimate the actual risk since a portion of the observed excess may be due to a number of biases (BEIR III). Thus these values should be regarded as upper bounds on the true risk. UNSCEAR 77 did not alter the estimate of 230 deaths per 10^4 population *in utero* per Gy given in its earlier 1972 report from leukemia and other childhood cancers combined. This estimate is equivalent to lifetime population risks of 1.2 cases (yielding 80 years of life lost) each of leukemia and other fatal cancers per 10^4 per Gy. We have used these alternative values for the central estimates and lower bounds for cancers due to *in utero* exposure.

2.4.10 Risks from Whole-Body Irradiation

Even though the doses received in a nuclear power plant accident will vary by tissue and organ, it is important to compare our estimate of the total mortality from all cancers other than leukemia and bone cancer, obtained by summing the site-specific lifetime risk estimates obtained in Table 2.2, with that obtained directly from the Japanese Life Span Study.

The absolute linear risk coefficient for the period 1955-1978 based on average organ dose and an RBE of 10 can be calculated from current data on the Japanese survivors (Kato and

Schull, 1982). If the value obtained (4.5 deaths per 10^4 PY per Sv) is multiplied by 1.23 to correct for under-diagnosis of cancer (BEIR III), a coefficient of 5.5 deaths per 10^4 PY per Sv results. The relative risk coefficient obtained by expressing the number of radiation-induced cancers obtained as a fraction of spontaneous cancers based on U.S. rates 10-33 years after follow-up is 23% per Gy. The lifetime absolute risk estimate is 185 deaths per 10^4 per Gy while the lifetime relative risk is 339 deaths per 10^4 per Gy.

These risks are slightly lower than the total of the linear lifetime risk estimates for all cancers other than leukemia and bone presented in Table 2.2. These totals are a lifetime absolute risk estimate of 244 deaths per 10^4 per Gy and a lifetime relative risk estimate of 419 deaths per 10^4 per Gy. In calculating these totals, the non-age-specific breast cancer estimates and the smaller relative lung cancer estimates have been used. Cancers resulting from *in utero* exposure as well as leukemia and bone cancers were excluded. Absolute lifetime risk estimates for thyroid cancer have been included in both cases. If the larger estimates for breast and lung are used, the two totals are 248 and 517 deaths per 10^4, respectively.

2.5 Comparison with Reactor Safety Study Model for Latent Somatic Effects

Since the publication of the Reactor Safety Study (1975), additional epidemiological data for estimating the risk of cancer due to radiation have become available. Consideration of these additional data has led to a number of modifications of the model previously used to estimate latent somatic effects. First, risks for cancers other than leukemia and bone are assumed to persist for a lifetime, rather than 30 years as assumed previously. Second, while all risk estimates for the earlier model were based on an absolute risk model, the revised model bases central estimates and upper bounds for several cancer sites, including breast, lung, and gastrointestinal cancer, on the relative risk projection model. Third, the most recent epidemiological data has been considered in determining numerical risk coefficients. Fourth, the dose reduction factors used in the earlier report in obtaining central estimates have been modified slightly, and a continuous linear-quadratic function replaces the previous discontinuous function. Fifth, the quadratic lower bound estimate used in the earlier report has been replaced with a linear-quadratic function (different from that used for the central estimate). Sixth, a different approach for estimating cancer incidence has been implemented; and finally, estimates of the years of life lost and years of life lived after cancer occurs have been added. There are other minor differences, but the above represent the most important differences in the two models.

2.6 Computation of Lifetime Risk Estimates

This section describes the calculations needed to determine lifetime risks using both relative and absolute models. Results are expressed as the number of cancer deaths (or cases) that are expected to occur in a population of ten thousand persons exposed to one Gy, followed from the onset of exposure until the end of life. This number, b, can then be multiplied by the dose D received by a particular segment of the population residing in a specific region to obtain linear or upper bound estimates. Linear quadratic estimates can be obtained by multiplying by reduction factors of the form $a+cD$, as described in Section 2.3.1. Results can then be summed over regions, weighting by the number of persons residing in each region, to obtain the total number of cancers expected.

The following notation is needed. Let f_j denote the fraction of the population in age group j where age groups will ordinarily be considered in five-year intervals (up to age 95). The f_j are obtained from the age distribution of the population of the U.S. in 1978. Let y_{jk} be the expected number of life years lived in age group k for a person known to be alive in age group j, $k > j$. Then $y_{jk} = 5\,\frac{{}_5L_{5k}}{{}_5L_{5j}}$ where ${}_5L_{5k}$ is defined as the number of person-years lived from age $5k$ to $5k+5$ in a standard life table population. The ${}_5L_{5k}$ are obtained from 1978 U.S. life tables (see Appendix D). Let A indicate the absolute risk expressed as excess cancer cases per 10^4 PY per Gy and let R indicate the comparable relative risk expressed as a per-Gy fractional increase in spontaneous rates. Finally, let λ_k denote the spontaneous rate obtained from the 1973 U.S. mortality data for the cause of death being evaluated (see Appendix D).

Under the assumption of a lifetime absolute risk model with a minimal 10 year latent period, the lifetime risk can be obtained by multiplying the risk coefficient A by the factor

$$P = \sum_j f_j [0.5\, y_{jj+2} + \sum_{k=j+3} y_{jk}]. \tag{2.1}$$

(The adjustment factor of 0.5 is needed because not all years in this age group will occur before the 10 year latent period.) The quantity in brackets is the expected number of years of life remaining less the latent period. The factor P can be thought of as the number of deaths per 10^4 population that would result from an effect of 1.0 death per 10^4 PY per Gy. The mean number of years of life lost following a death can be estimated by the ratio

$$Q = \sum_j f_j \left[0.5\, y_{jj+2} \frac{e_{j+2} + e_{j+3}}{2} + \sum_{k=j+3} y_{jk} \frac{e_k + e_{k+1}}{2} \right] / P \tag{2.2}$$

where e_k is the expected number of years of life remaining for a person at the beginning of the kth age group. The value $(e_k + e_{k+1})/2$ should approximate the number of years of life remaining for the *average* person in age group k. For the oldest age group (95+) the average expectation can be calculated from an unabridged life table.

If the y_{jk} and e_k are obtained from a 1978 life table, while the f_j are obtained from the 1978 U.S. population, the value of P will be 33.66 person-years while Q will be 24.46 years of life lost per death. To obtain the linear estimate of the lifetime risks per Gy, one would multiply P by the appropriate annual risk coefficient, A, for the deaths (or cases) per 10^4 per Gy. This product would then be multiplied by Q to obtain the years of life lost per 10^4 persons per Gy. For example, the absolute risk coefficient for gastrointestinal cancers is 2.7 deaths per 10^4 PY per Gy yielding lifetime risks of $2.7 \times 33.66 = 91$ (90.87) deaths per 10^4 per Gy and $90.87 \times 24.46 = 2223$ years of life lost per 10^4 per Gy. In Table 2.10, values of P are given for the entire population, excluding deaths under age 40 (for lung cancer calculations), and with a minimal 5-year latent period (for thyroid cancer calculations). Values of Q, years of life lost per death, are presented in Table 2.11. Values of P based on female life tables and the age distribution of females are also presented and are used for breast cancer calculations.

Table 2.10 Deaths per 10^4 Population and Their Distribution by Age at Exposure[a]

		Age at Exposure					Total
		0-9	10-19	20-29	30-39	≥40	
Proportion of population in age group[b]	Total	0.147	0.181	0.175	0.133	0.363	1.000
	Female	0.141	0.174	0.172	0.132	0.385	1.000
Deaths based on an effect of 1.0 per 10^4 PY							
Total		8.75	8.97	7.12	4.18	4.64	33.66
Excluding deaths occurring under 40 years of age		5.15	6.34	6.23	4.18	4.64	26.55
Female[c] excluding deaths occurring under age 30		6.81	8.41	7.61	4.55	5.50	32.87
Deaths occurring 2-27 years following exposure		3.64	4.43	4.26	3.15	6.05	21.53
Deaths occurring 5 or more years following exposure		9.48	9.86	7.98	4.84	6.14	38.31
Spontaneous deaths[d] due to							
Breast cancer[c]		46.01	58.78	56.43	40.93	64.89	265.0
Lung cancer[e]		64.91	79.93	78.45	59.23	90.09	372.7
Gastrointestinal cancer		79.55	97.88	95.74	72.65	138.80	484.6
Other cancers (excluding types above plus leukemia, bone, thyroid, skin, and prostate)		82.30	100.71	97.62	72.83	127.13	480.6

[a]Unless noted otherwise, numbers are based on deaths that would occur 10 years following exposure until the end of life. Numbers are expressed per 10^4 total population. (To obtain numbers expressed per 10^4 population within a particular age at exposure group, entries must be divided by the proportion in the age group).

[b]Based on U.S. population, 1978.

[c]Expressed per 10^4 women. Deaths occurring under 30 years of age are excluded.

[d]Based on U.S. Vital Statistics, 1978.

[e]Deaths occurring under 40 years of age are excluded.

Table 2.11 Years of Life Lost Per Death by Age at Exposure[a]

Model	Age At Exposure					All Ages[d]
	0-9	10-19	20-29	30-39	⩾40	
Absolute Risk						
All deaths occurring 10 or more years following exposure	31.98	27.36	22.99	18.71	12.11	24.46
Excluding deaths occurring under 40 years of age	20.59	20.59	20.59	18.71	12.11	18.81
Female excluding deaths occurring under 30 years of age	26.42	26.42	24.34	19.94	12.80	22.76
Deaths occurring 2-27 years following exposure	55.54	46.14	37.33	28.84	15.59	34.88
Deaths occurring 5 or more years following exposure	34.31	29.65	25.23	20.85	13.54	26.19
Relative Risk						
Breast cancer[b]	17.88	17.88	17.60	16.44	11.40	16.01
Lung cancer[c]	15.26	15.26	15.26	14.90	11.52	14.30
Gastrointestinal cancers	12.67	12.64	12.54	12.17	9.48	11.65
Other cancers (excluding types above plus leukemia, bone, thyroid, skin, and prostate)	14.73	14.49	14.11	13.40	10.05	13.11

[a]Unless noted otherwise, numbers are based on deaths that would occur 10 years following exposure until the end of life.

[b]Deaths occurring under 30 years of age are excluded.

[c]Deaths occurring under 40 years of age are excluded.

[d]From population with U.S. age structure (1978).

To obtain lifetime relative risk estimates, one must first calculate the relative risk coefficient from the absolute risk coefficient and U.S. spontaneous rates. (An exception is breast cancer for which relative risk estimates have been obtained directly from the study population.) This calculation is made as follows. The relative risk is determined as the value of R that will yield the same number of deaths as the absolute model over the follow-up period upon which the estimate A is based. This value will be the number of radiation-induced deaths (r) based on the absolute model expressed as a fraction of the number of spontaneous deaths (s) occurring during the relevant follow-up period. For Japanese absolute risk estimates based on the time period January 1, 1955, to January 1, 1979 (corresponding to 9.5-33.5 years of follow-up), we would have:

$$r = A \sum_j g_j \left[0.6\ y_{jj+2} + \sum_{k=j+3}^{j+6} y_{jk} + 0.2\ y_{jj+7} \right]$$

and

$$s = \sum_j g_j \left[0.6\ y_{jj+2} \lambda_{j+2} + \sum_{k=j+3}^{j+6} y_{jk} \lambda_{jk} + 0.2\ y_{jj+6} \lambda_{j+7} \right]$$

where the g_j indicate the fraction of the Japanese Life Span Study population in age group j at the time of exposure. These fractions (obtained from Kato and Schull, 1982) are 0.191 for those who were 0-9 years at exposure, 0.215 for 10-19 years, 0.199 for 20-34 years, 0.233 for 35-49 years, and 0.161 for 50 years and older. To obtain the g_j for 5-year age groups, the broader age groups were subdivided proportionally to the U.S. life table population. Using the Japanese distribution is important since at the time of the bombings the Life Span Study population was considerably younger than the 1978 U.S. population. Age-at-exposure-specific risks can be obtained by calculating r and s separately for various age-at-exposure groups; these groups may be broader than 5-year age groups and thus may include several values of j.

Lifetime relative risk estimates are obtained by multiplying the coefficient R by the number of spontaneous deaths that would be expected to occur per 10^4 population in the period more than 10 years after exposure. This number is given by

$$S = \sum_j f_j \left[0.5 \lambda_{j+2} y_{jj+2} + \sum_{k=j+3} \lambda_k y_{jk} \right] \tag{2.3}$$

The mean number of years lost following a death is given by

$$T = \sum_j f_j \left[0.5 \lambda_{j+2} y_{jj+2} \frac{e_{j+2} + e_{j+3}}{2} + \sum_{k=j+3} \lambda_k y_{jk} \frac{e_k + e_{k+1}}{2} \right] / S \tag{2.4}$$

The expressions given in equations (2.3) and (2.4) have been evaluated for four major cancer categories with the results given in Table 2.10, and can be used to obtain lifetime linear

relative risk estimates in a manner analogous to that described for the absolute model. For example, the lifetime risk estimates for gastrointestinal cancers based on the coefficient 39% per Gy are $0.39 \times 484.6 = 189.00$ deaths per 10^4 per Gy and $189.00 \times 11.65 = 2202$ years of life lost per 10^4 per Gy.

If age-at-exposure-specific estimates are desired, they can be obtained by multiplying the age-at-exposure-specific terms, which are presented in Tables 2.10 and 2.11, by separate coefficients A_j or R_j. For example, the age-at-exposure-specific relative risk estimate for breast cancer is obtained as $(103\% \times 104.8) + (42\% \times 162.3) = 175$ deaths per 10^4 per Gy. With the exception of breast cancer, no attempt is made to calculate gender-specific estimates. Although it is recognized that risks of radiation-induced thyroid cancer, and possibly other cancers, differ by gender, the total population risk is not likely to be seriously distorted by making calculations in a non-gender-specific manner.

Other latent periods and risks assumed to persist for less than a lifetime can be obtained by modifying equations (2.1)-(2.4) in a straightforward manner. For calculating absolute risk estimates for leukemia and bone cancer, the number of deaths per 10^4 population that would result from an effect of 1.0 death per 10^4 PY per Gy for the time period 2-27 years following exposure is 21.53 per 10^4 while the number of years of life lost per death is 34.88, as indicated in Tables 2.10 and 2.11.

Incidence estimates using the relative risk model can be obtained by substituting incidence rates for mortality rates λ_k in expression (2.3). Incidence estimates using the absolute risk model are calculated so that the ratios of the incidence and mortality are the same for the absolute and relative risk projections. The number of years lived following cancer diagnosis can be calculated by applying (2.4) with incidence rates and then subtracting the corresponding number of years of life lost. Tables 2.12 and 2.13 contain the information needed for obtaining lifetime incidence estimates.

For example, the lifetime relative risk incidence estimate for gastrointestinal cancers is obtained by multiplying the relative risk coefficient, 39% per Gy, by the number of spontaneous cases given in Table 2.12, 825.9, yielding 322.1 cases per 10^4 per Gy. The absolute risk estimate for incidence is then (322.1/189.0) x 90.87 or 154.9 cases per 10^4 per Gy, where 189.0 and 90.87 are the respective relative and absolute mortality estimates given in Table 2.2. The years of life lived after cancer occurrence for the relative risk model is obtained as 322.1×5.34 (from Table 2.13) = 1720. For the absolute risk model the number of years of life lived after cancer occurrence is $(154.87 - 90.87) \times 24.46$ (from Table 2.11) = 1565.4 per 10^4 per Gy.

No adjustment is made to account for the fact that a person cannot die twice of a radiation-induced cancer. Such adjustment would require separate calculations for each dose level, and would also require that deaths from all cancer types be considered in the calculations for any particular site. Because such adjustment would have a negligible effect on risks being considered here, these added computational difficulties did not seem necessary.[1]

[1] To investigate this question, lifetime risks for a population exposed to 0.1 Gy were made on the assumption that mortality from all cancers was increased by 50% per Gy. In this situation, adjustment by decreasing the number of person-years at risk to account for earlier radiation-induced cancer deaths, lowered the estimated total number of radiation-induced deaths by less than 1%. Even in the more extreme situation of a population exposed to 1 Gy, such adjustment decreased the lifetime risk estimate only by about 10%, a fairly small amount relative to other uncertainties.

Table 2.12 Spontaneous Cancer Cases Per 10^4 Population and Their Distribution by Age at Exposure[a,b]

Cancer Type	Age At Exposure					Total
	0-9	10-19	20-29	30-39	≥ 40	
Breast[c]	137.52	169.72	167.60	117.73	172.29	764.86
Lung[d]	72.58	89.36	87.71	66.02	97.85	413.51
Gastrointestinal	137.39	168.97	165.07	124.77	229.74	825.94
Other (excluding types above plus leukemia, bone, thyroid, skin, and prostate)	168.78	205.11	196.19	143.47	223.26	936.81

[a]Unless noted otherwise, numbers are based on deaths that would occur 10 years following exposure until the end of life. Numbers are expressed per 10^4 total population. (To obtain numbers expressed per 10^4 population within a particular age at exposure group, entries must be divided by the proportion in the age group).

[b]Based on Cancer Incidence and Mortality in the United States, 1973-1977 (SEER)

[c]Expressed per 10^4 women. Cases occurring under 30 years of age are excluded.

[d]Cases occurring under 30 years of age are excluded.

Table 2.13 Years of Life Lived After Cancer Diagnosis Per Case by Age at Exposure Under Relative Risk Projection Model[a]

Cancer Type	Age At Exposure					All Ages[d]
	0-9	10-19	20-29	30-39	≥40	
Breast[b]	13.71	13.71	13.34	11.84	7.55	11.95
Lung[c]	1.97	1.97	1.97	1.82	1.07	1.73
Gastrointestinal	5.95	5.92	5.83	5.57	4.06	5.34
Other (excluding types above plus leukemia, bone, thyroid, skin, and prostate)	9.92	9.51	8.86	8.01	5.11	8.17

[a]Unless noted otherwise, numbers are based on deaths that would occur 10 years following exposure until the end of life.

[b]Deaths occurring under 30 years of age are excluded.

[c]Deaths occurring under 40 years of age are excluded.

[d]From population with U.S. age structure (1978).

Without this adjustment, risks are slightly overestimated.

Finally, we note that the calculation of lifetime risks requires consideration of three types of exposure: the initial external exposure received from the passing cloud, chronic exposure resulting from ground contamination, and chronic exposure resulting from inhaled and ingested radioactive materials. For the first two types, the age at exposure distribution will be the same provided a stationary age distribution is assumed. Thus the model above can be used, although for the second type of exposure it is necessary to assume that the dose rate is such that only the linear term of the linear quadratic is needed.

This assumption about dose rate is also made for the third type of exposure. However, the risks due to this third exposure pathway must be treated separately. Radioactive materials inhaled at the time of the accident will continue to decay and generate doses for years after the accident. However, the age structure of the population affected will change over time. In treating such exposure, the assumption is made that all exposure received during a given decade after the accident occurs at the beginning of a particular decade. The effects of exposure occurring as a result of dose received in the n^{th} decade after the accident can be calculated by omitting persons exposed at ages less than 10n from the calculations. For example, the population receiving doses two decades after the accident from radioactive materials inhaled or ingested at the time of the accident would not include persons under 20 years of age. The needed person-years and spontaneous deaths for these calculations can be obtained from Tables 2.10-2.13.

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Appendix 2A

EXAMPLE CALCULATIONS

To illustrate the application of the formulae in Section 2.6, we show the details in calculating the quantities in expressions (2.1), (2.2), (2.3), and (2.4) for the age at exposure groups 20-24 ($j = 4$) and 25-29 ($j = 5$) for mortality from cancers of the digestive system. The quantities ${}_5L_{5k}$, $y_{jk} = 5\,\frac{{}_5L_{5k}}{{}_5L_{5j}}$, $\dot{e}_k$, $\frac{\dot{e}_k + \dot{e}_{k+1}}{2}$, and λ_k (for cancers of the digestive system) are shown in Table 2A.1. The fraction of the population aged 20-24 (f_4) is 0.093 while the fraction aged 25-29 (f_5) is 0.082 (based on the 1978 U.S. population).

Expression (2.1): The term for $j = 4$ (age 20-24) is given by

$$f_4 \left[0.5\, y_{46} + \sum_{k=7} y_{4k} \right]$$

$= 0.093\ [0.5 \times 4.93 + 4.89 + \ldots + 0.13] = .093\ (42.79) = 3.98$ deaths based on an effect of 1.0 per 10^4 PY in a total (all ages) population of 10,000. The term for $j = 5$ is 0.082 (38.13) = 3.13. Thus the contribution for the age group 20-29 is 3.98 + 3.13 = 7.11, the entry in Table 2.10. (Rounding errors account for slight differences in the results given in this example, and results included in the tables, which were calculated using a computer program.)

Expression (2.2): The term for $j = 4$ in the numerator of this expression is given by

$$f_4 \left[0.5\, y_{46}\, \frac{\dot{e}_6 + \dot{e}_7}{2} + \sum_{k=7} y_{4k}\, \frac{\dot{e}_k + \dot{e}_{k+1}}{2} \right]$$

$= 0.093\ [0.5 \times 4.93 \times 43.4 + 4.89 \times 38.7 + \ldots + 0.13 \times 3.4] = 0.093\ (1025.6) = 95.38$. The term for $j = 5$ is 0.082 (829.3) = 68.00. The average years of life lost per death for those exposed at age 20-29 is given by (95.38 + 68.00) / 7.11 = 22.98 as given in Table 2.11. The years of life lost per death for all ages is obtained by summing the terms in the numerator of (2.2) across all exposure ages and dividing by 33.66, the value for expression (2.1).

Expression (2.3): The term for $j = 4$ is given by

$$f_4 \left[0.5\, \lambda_6\, y_{46} + \sum_{k=7} \lambda_k\, y_{4k} \right]$$

which equals 0.093 (545.5) = 50.73 while the term for $j = 5$ equals 0.082 (547.3) = 44.88. The

Table 2A.1 Data Needed for Illustrative Lifetime Risk Calculation

Age Index k	Age at Beginning of Interval 5k	Stationary Population in the Age Interval ${}_5L_{5k}$[a]	Years Lived in the Interval By Persons Alive at the Beginning of: the 4th Interval Y_{4k}	the 5th Interval Y_{5k}	Life Expectancy At Beginning of Interval ${}^0e_k$	Average Life Expectancy In Interval $\frac{{}^0e_k + {}^0e_{k+1}}{2}$	Baseline Risk λ_k[b]
0	0	492652	--	--	73.3	71.4	0.02
1	5	491312	--	--	69.5	67.1	0.01
2	10	490573	--	--	64.6	62.2	0.01
3	15	488960	--	--	59.7	57.4	0.02
4	20	485985	--	--	55.0	52.7	0.04
5	25	482735	4.96655	--	50.4	48.1	0.10
6	30	479538	4.93366	4.96689	45.7	43.4	0.24
7	35	475679	4.89395	4.92692	41.0	38.7	0.52
8	40	470041	4.83595	4.96852	36.4	34.2	1.18
9	45	461238	4.74538	4.77734	31.9	29.8	2.50
10	50	447647	4.60555	4.63657	27.6	25.6	4.31
11	55	427499	4.39826	4.42789	23.5	21.6	7.91
12	60	398024	4.09502	4.12259	19.7	18.0	13.31
13	65	358257	3.68583	3.71070	16.3	14.7	18.48
14	70	307056	3.15910	3.18038	13.1	11.8	26.68
15	75	241082	2.48034	2.49704	10.4	9.3	37.63
16	80	166202	1.70995	1.72146	8.1	7.3	46.74
17	85	110982	1.14182	1.14951	6.4	5.6	51.33
18	90	42322	0.43542	0.43836	4.8	4.2	51.33
19	95	12816	0.13186	0.13274	3.6	3.4	51.33

[a] Based on a stationary population with 100,000 live born per year. Source: Vital Statistics of the United States, 1978; Volume II, Section 5 "Life Tables", Table 5.1, p. 5.9. National Center for Health Statistics, Public Health Service, US DHEW, DHEW Publication No.(PHS) 81-1104, Hyattsville, MD 1980.

[b] Risk per 10,000. See Table B.4 "1978 Mortality Rates per 100,000 Population" in Appendix B of this volume.

sum is given by 95.61, the value found for age 20-29 under gastrointestinal cancers in Table 2.10.

Expression (2.4): The term in the numerator for $j = 4$ is given by

$$f_4 \left[0.5 \, \lambda_6 \, y_{46} \, \frac{\dot{e}_6 + \dot{e}_7}{2} + \sum_{k=7} \lambda_k \, y_{4k} \, \frac{\dot{e}_k + \dot{e}_{k+1}}{2} \right]$$

which equals 0.093 (6864.9) = 638.4, while the term for $j = 5$ is 0.082 (6835.7) = 560.5. Thus the years of life lost per death is given by (638.4 + 560.5) / 95.61 = 12.54, the value in Table 2.11 for the 20-29 age group for gastrointestinal cancers.

Chapter 3

GENETIC EFFECTS

S. Abrahamson, M. Bender, C. Denniston, and W. Schull

Executive Summary

In this chapter, we present a comprehensive analysis of the major classes of genetic diseases that would be increased as a result of an increased gonadal radiation exposure to a human population. The risk analysis takes on two major forms: the increase in genetic disease that would be observed in the immediate offspring of the exposed population, and the subsequent transmission of the newly induced mutations through future generations. The major classes of genetic disease will be induced at different frequencies, and will also impact differentially in terms of survivability and fertility on the affected individuals and their descendants. Some classes of disease will be expected to persist for only a few generations at most. Other types of genetic disease will persist through a longer period, an average of 5 to 10 generations, before selection operates to "sieve them out" of the reproducing populations. For the most part, about 50% of the newly induced mutations that appear in the first generation will be manifest within the first 3 to 5 generations.

The classes of genetic diseases studied are: dominant gene mutation, X-linked gene mutation (that is, sex-linked mutations), chromosome disorders (changes in the normal number or structure of chromosomes) and multifactorial (polygenic) disorders which involve the interaction of many mutant genes and environmental factors. For each of these classes we have derived the general equations of mutation induction for the male and female germ cells of critical importance in the mutation process, that is, the spermatogonial cells of the male and the immature oocyte cells of the female. The frequency of induced mutations will be determined initially by the dose received, the type of radiation and, to some extent at high dose, by the manner in which the dose is received, that is, whether the total dose is received over a short period of time (within hours, an acute dose), versus the same total dose accumulated over perhaps months or years (a protracted or chronic dose). More mutations are produced with an acute, high total dose than from the same dose protracted over a long time. Secondarily, other biological factors will affect the recovery of these mutations.

It is commonly accepted procedure to express the number of new cases of genetic disease induced in some population of fixed size in comparison to some baseline or unit dose. A population of one million people of all ages would be expected (based on 1978 demography) to produce about 480,000 children in the next generation. If that population were to receive an additional dose of 0.01 Gy (1 rad), this would result in about 30 new cases of genetic disease in that period. Of these, some 15 children would suffer from diseases of a dominant gene mutation origin, such as Huntington chorea, hypercholesterolemia or achondroplastic dwarfism, to name a few of the hundreds of such recognized diseases. Some of these diseases would be apparent at birth while others would become manifest at various ages. About 5 children (males) would show some form of X-linked disorders; muscular dystrophy, hemophilia or the inability to produce antibodies (agammaglobulinemia) are 3 of some 200 kinds of such diseases. About 5 children would be chromosomally abnormal (aneuploids) suffering from predominantly Down syndrome, Klinefelter or Turner sex chromosome anomalies. About 6 additional children would manifest other chromosome anomalies that resulted from chromosome breakage leading to less than the normal amount of genetic material. These latter cases generally suffer severe physical and mental disabilities and have very shortened life spans. These effects result from an event known as an unbalanced translocation. Some of the siblings of these children will have a balanced chromosome rearrangement, however, and while usually appearing normal, will transmit the unbalanced state to their children. Such diseases will persist on the average for only one or two generations. The aneuploid types

(Down syndrome and others) are not usually reproductive and therefore will not transmit their disorders to subsequent generations. The dominant and X-linked disorders will be selected against but will generally persist for 5 or 6 generations. Put another way, in addition to the 15 cases of dominant diseases appearing in the first generation, about 12 additional cases will be observed (that is, transmitted) in the second generation, 9 additional cases will be transmitted in the third, and so forth; that is, fewer cases will be transmitted in each successive generation until they are all eliminated. Some 70 individuals in all will have dominant disorders in the approximate 5 or 6 generations over which these mutations persist.

With respect to the irregularly inherited polygenic diseases, little can be said about their precise dynamics save that they are estimated to persist for an average of 10 generations. Through the course of that time, about 60 to 70 children would be predicted to be affected by our central estimate, but a much wider range of uncertainty exists.

These 30 newly induced cases in the first generation represent our central or best estimate. There would be almost 51,000 cases of genetic disorder in this same population of children that were unassociated with the radiation experience. This represents the current incidence of genetic disease. There is, of course, a range of uncertainty associated with each genetic endpoint. The lower estimate of the total number of affected children in the first generation is about 6 and the upper estimate would be about 130. The cumulative number of cases of genetic disease over the next 10 generations would be about 185. This represents the central estimate.[2] Clearly, advances in medical and other technologies and changes in demographic structure could influence these estimates in profound ways. Therefore, caution should be exercised in accepting this figure and in interpreting the lower and upper bounds we have developed.

The starting point for the above conclusions is based on the earlier analyses provided by the BEIR I and BEIR III reports of the National Academy of Sciences (NAS, 1972, 1980) and the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1977, 1982). We have modified their analyses in several important respects as a result of new scientific information and analytic methodologies. We have employed equivalent induced mutation rates for the two sexes and we have developed an induced X-linked mutation rate for humans. In addition, we have developed a general set of mutation induction equations for each class of genetic event and this has permitted us to calculate the yield under a wide variety of doses and dose rates. These equations have been incorporated into a computer model using existing demographic data to predict outcomes of radiation accidents for 5 year intervals through the next 150 years (approximately 5 generations). This phase is an extension of the analysis initiated by the Reactor Safety Study group (1975). We have adjusted the maternity rate to provide a stable population size over that time period. *Were the population size to decrease (increase), the absolute number (but not the proportion) of mutant cases would, of course, be reduced (increased) accordingly.*

We have also incorporated the UNSCEAR impairment concept (1982) to develop a genetic risk calculation in terms of effective years of life lost for each class of genetic disease. While perhaps still a crude expression of the impact of genetic disease, this approach has the advantage of allowing a comparison of the genetic and somatic disorders (both spontaneously-occurring and radiation-induced) with the same index of harm. Thus it

[2] Ten generations are chosen to allow complete manifestation of the irregularly inherited diseases; the other classes of diseases considered will have been expressed to a great extent in the first five or six generations.

appears that while the number of cases of genetic disease-induced per unit dose in the first generation may be about one third the number of cases of cancer induced in their parents, the impact in terms of the years of effective life lost is about the same. This is because many of the genetic disorders are manifest at birth while the somatic effects usually exert their impact later in life. The effective years of life lost for the 30 cases induced by a uniform dose of 0.01 Gy (1 rad) is 1130 (about 38 years of life lost per case). This can be compared with 1,830,000 years of life lost in the same group (480,000 births) as a result of genetic disorders unassociated with radiation. The impact over all time would be about 6000 years of life lost (185 cases $\times$ 33 years of life lost per case) since the most severe cases would not reproduce beyond the first generation.

We have used the modeling analyses to predict the outcomes for two nuclear power plant accident scenarios, the first in which the population receives a chronic dose of 0.1 Gy (10 rad) over a 50 year period, the second in which an equivalent population receives acute dose of 2 Gy. In both cases the analyses are projected over a period of five generations.

Finally, we have used the mortality data of the children and doses to their parents from the Hiroshima-Nagasaki atomic bombings to predict the expected yield of cases among 16,713 children of exposed parents on the basis of our central risk estimates (Schull, Otake, and Neel, 1981). Clearly if the observed and predicted first generation values are not in reasonable agreement, then serious questions could be cast on the mutation equations we have derived primarily by extrapolating the results from animal studies to humans. Although we note that the dosimetry for the Japanese survivors of the atomic bombings is presently undergoing revision, we believe that more than adequate agreement is observed. Only if there were substantially increased estimates of the doses to the high dose groups would there be major change in our projections. A change in the dose by a factor of 3 in the low dose range would have little impact on the estimated number of cases while a 25% change at the high dose range would have a considerably greater impact on our estimates.

In conclusion, we believe that an appropriate set of genetic risk estimates can be developed to encompass the wide range of scenarios resulting from nuclear power plant accidents or other forms of population exposure. If no individual in the population receives more than an 0.5 Gy gonadal dose, then the average population dose can be employed to determine the genetic risk because in this dose range the response is proportional to the average dose. If some individuals receive high doses acutely, the more general linear-quadratic dose response equations must be evaluated for each subset of the population including persons with such doses.

3.1 Introduction

Unlike estimates of somatic risk from exposure to ionizing radiation, almost all of which have been derived from a number of human studies, human genetic risk estimates, in the main, are based on extrapolations from animal data. The spermatogonial cells of the mouse have served as a surrogate for the equivalent human germ cell stage of greatest importance for genetic effects in the male. Unfortunately, there appears to be no mouse surrogate system for the female. What limited human data exist come primarily from studies on the offspring of the survivors of the atomic bombings of Hiroshima and Nagasaki (Schull *et al.*, 1981a,b). To date these studies (to be discussed in more detail below) do not demonstrate an increased incidence of genetic defects in the survivors' children. They do, however, allow a rough estimate of the upper bounds for induction of such effects. Where applicable these data will be used in this report to determine if risk estimates derived from extrapolation of animal experimental data are reasonable.

The authors of the Reactor Safety Study (NRC, 1975) relied heavily on information presented in the 1972 BEIR I Report (NAS, 1972) in developing their estimates of genetic risks. Since that time, the 1980 BEIR III Report has been published (NAS, 1980). We will make considerable use of the latter report, as well as other information subsequently made available (NCRP, 1980; Oftedal & Searle, 1980; and UNSCEAR, 1982), information which, we believe, makes it possible to derive more reliable risk estimates.

In calculating our estimates we will (as did the authors of the Reactor Safety Study) confine ourselves to risks arising as a consequence of gonadal exposures to low-LET radiation. Particular concern has been expressed by some analysts over the possible greater mutational hazard of exposure from plutonium, an alpha-emitting radionuclide that could be dispersed during an accident and possibly ingested or inhaled by the affected population. The question of plutonium genotoxicity was addressed in the BEIR III Report and the writers of that report concluded that plutonium exposure does not, in fact, constitute a particular genetic hazard under such circumstances (NAS, 1980).

It has been estimated that about 50% of all the genetic damage introduced by radiation exposures resulting from a nuclear power plant accident will be manifest within the first three to five subsequent generations with the remaining damage dispersed over future generations (NAS Committee on Environmental Mutagens, 1982). We believe it is appropriate to concentrate our attention on the estimate of induced disease burden produced in the more immediate generations because technological, demographic and environmental changes can have a profound influence on whether the predicted long range effects will ever be manifest.

3.2 Estimates of the Current Incidence of Genetic Disease

This chapter is concerned with those genetic disorders that are expected to increase with increased exposure to radiation, namely, the diseases which have an induced mutation rate component. *Single-gene disorders* (autosomal dominant and recessive and X-linked traits), *multifactorial diseases,* and *chromosome anomalies* make up the three major categories of interest. The current incidence of these traits is presented in Table 3.1, and a tabular listing of the major representative diseases in each class is presented in Appendix 3E. The listing is taken from the UNSCEAR Reports of 1977 and 1982.

Table 3.1 Numbers of Naturally Occurring and Radiation-Induced Genetic Disorders In a Population of One Million, Accourding to the BEIR III Report Analysis and According to the Present Analysis. Assumes a 0.01 Gy dose.

Type of Disorder	Normal[a] Incidence	BEIR III Report[b]		This Study (Central Estimates)[c]	
		First Generation[d]	All Generations[e]	First Generation[d]	All Generations
Single-gene	4800	3 - 30	20 - 100		
Autosomal Dominant				15[f]	70
X-Linked				5	30
Irregularly Inherited	43200	-	10 - 400	-[f]	70[g]
Chromosome Aberrations[h]	2880	<5	~5		
Aneuploidy				4	5
Unbalanced Translocations				6	10
TOTALS[i]	50900	-	-	30	185

[a] For a total population of 10^6 persons (16,000 live births per year) for 30 years (480,000 live births).

[b] Cases expected in each generation of children from a population of 10^6 persons each receiving a dose of 0.01 Gy. Assumes 30 year intergenerational interval and birthrate of 16,000 per year per 10^6 persons, or 480,000 children per generation.

[c] Calculated using the computer program described in Appendix 3G based on 1978 demography, which assumes a projected birthrate (births/year) of 16,000 for each of the first 30 years, 15,600 for each of the years 30 through 59, and 15,000 for years 60 through 89. For method of calculation, the single value is the geometric mean of the range of values presented in the text.

[d] Estimated directly from measured phenotypic damage or from observed cytogenic effects.

[e] Based on doubling dose of 0.50 - 2.50 Gy, chronically delivered. Actually the BEIR III estimate was expressed as the equilibrium risk due to a dose of 0.01 Gy per generation. However, numerically the equilibrium risk is equal to the integrated risk over all future generations from a single dose of 0.01 Gy.

[f] First generation of irregularly inherited incidence included within first generation of single-gene incidence.

[g] Based on doubling dose of 1 Gy and 10 generations mean persistence time, which is very uncertain.

[h] Includes only aberrations expressed as congenital malformations resulting from unbalanced translocations, 1000; and from aneuploidy (nuberical aberrations), 5000; equilibrium time 1-2 generations and 1 generation respectively.

[i] Totals rounded off to avoid perecption of false precision.

The BEIR III committee (NAS, 1980) estimated that 10.7% of all liveborn individuals suffer or will suffer from serious genetic disease (primarily of spontaneous origin) at some point in their lives. This estimate was derived from epidemiological studies in British Columbia (Trimble and Doughty, 1974). This is an increase of nearly two-fold over the estimate of the BEIR I Report, and results from the recognition of the much larger contribution of the class of irregularly inherited genetic diseases, that is, multifactorial disorders.

The estimated incidence of the other major classes of genetic disease as presented in the BEIR III Report (NAS, 1980) remains essentially unchanged. Recently, Gofman (1981) has criticized the genetic risk estimates in the 1977 UNSCEAR and the 1980 BEIR III Reports, claiming they grossly underestimate the true effect. We, however, believe that the BEIR III and UNSCEAR Reports, in general, properly estimate the genetic effects of human populations to radiation (See Appendix 3A for further discussion).

3.3 Nature of Genetic Damage

Genetic information is encoded within the nucleus of the cell, in genes that are large specific sequences of deoxyribose nucleic acid (DNA). There are many thousands of such genes in man and each has its own specific DNA sequence made up of thousands of subunits called nucleotides. A specific alignment of genes, usually several hundred or more, exists on a specific structure called a chromosome. The alteration (substitution, deletion or addition) of any one or more nucleotide subunits may lead to an altered function of the gene and thus to an observable mutant when contributed by the germ cell of a parent. This represents a single gene mutation. It is called a *dominant mutation* if it exerts an effect in the presence of an equivalent normal gene which was contributed by the other parent. It is called a sex-linked mutation (more accurately an X-linked mutation) when it is found on the X chromosome (males have only one X chromosome, females have two); thus the mutation on the X-linked gene will invariably manifest an effect in males (act as a dominant), for example hemophilia, but the same mutation will usually not produce an effect in females when a normal form of the gene was on the other X chromosome. Of all liveborn, 1% are affected by dominant and X-linked diseases at some time in their lives.

Regularly inherited *recessive* gene disorders require that the pair of genes (present on an autosome, a non-sex-chromosome) contributed, one from each parent, both be mutant in order for the disease, for example, cystic fibrosis, to be manifest. At present, some 0.4% of all liveborn are found to suffer from such recessive diseases. Newly induced recessive gene mutations are not expected to produce significant numbers of diseases over the period of our analysis. In fact, most newly arising recessive mutations are not expected to manifest an effect (disease) in less than about 100 generations (3000 years). Secondly, many recessives are thought to be partially dominant and are likely to be eliminated from the population through heterozygous effects before becoming homozygous. They then are included with the dominant group. Further, since societal advances, environmental influences, and reproductive patterns can have a profound impact on moderating the recessive disease burden, we believe our concern should be more focused, that is, over the first five generations. For these reasons, recessive mutations are excluded from further detailed consideration as has been done by those who have prepared all other evaluations of risk (NAS, 1972, 1980, and UNSCEAR, 1982). In Appendix 3C, we have provided estimates of induced damage from these effects (for the exposure conditions to be discussed later).

Evidence supports the view that the majority of radiation-induced mutations in higher organisms are tiny, usually (but not always) submicroscopic deletions or other rearrangements (inversions, insertions, etc.) encompassing parts of one or more genes. Single nucleotide changes induced by irradiation appear to be extremely rare; this is in contrast to chemically induced mutations. Thus the nature of the radiation-induced gene mutational event, a breakage process, determines the shape of the dose-induction response curve (see below).

Multifactorial diseases or *irregularly inherited diseases,* the largest class, represent a more complex inheritance pattern for which some combination of different mutant genes is required for an effect to be manifest. Included within this class are congenital malformations, constitutional and degenerative diseases. In addition, environmental conditions may influence the ultimate manifestation of each specific disease and as we learn to control the environmental influences, we can expect to reduce the manifestation of many of these diseases. However, recent developments, for example, in the understanding of the membrane transport of materials such as lipids and sodium-potassium, suggest that the role of genetic factors in hypertension and atherosclerosis may be larger and simpler than previously thought (Garay *et al.*, 1980, Canessa *et al.*, 1980). These groups of genetic and, in some cases, quasi-genetic diseases affect approximately 9% of all liveborn. However there is considerable uncertainty in this 9% value, depending upon which diseases are included in the analysis. The value of 9% was adopted by BEIR 1980.

Chromosome anomalies (numerical changes) or *aberrations* (structural changes) are two major classes of genetic disease. There are 23 pairs (or 46 in all) of chromosomes present in most normal somatic cells of the human body, with one member of each pair coming from the sperm and the other from the egg that produced the individual. When the process of sperm or egg cell production goes awry, it is possible for these cells to have a misdistribution of chromosomes either gain or loss (called nondisjunction) such that, for example, 24 or 22 chromosomes are present in one of the germ cells involved in fertilization. The fertilized egg will then contain 47 or 45 chromosomes, rather than the normal 46. Which specific chromosome of the set is involved determines whether the abnormality results in spontaneous abortion or an affected liveborn. Such abnormal individuals are known as aneuploids as, for example, in Down syndrome.

Chromosomes are susceptible to breakage and subsequent structural rearrangements of parts between different chromosomes. New alignments of genes within the same chromosome are also possible. When these structural changes occur in the germ line they can be transmitted to the offspring in such a manner that a chromosome set will contain either too little or too much of the necessary genetic information. Such imbalance may lead to a large variety of genetic disorders, depending on which specific chromosomes and genes are involved. Collectively, about 0.6% of liveborn infants will have a (serious) chromosome disorder, but this number varies with the demographic characteristics of the population because of the maternal age-dependency of chromosomal nondisjunction.

3.4 Radiation Risk Estimates: Low Doses

In the context of this report we employ the term *low dose* to mean a dose of 0.5 Gy or below, since this range of doses is believed to lie on the linear (dose-rate independent) portion of the linear-quadratic dose-response curve and the resultant biological effect from a given dose in this range should thus not be significantly influenced by changes in dose rate. Above

0.5 Gy the yield of biological effects of interest may be markedly affected by dose rate (the manner in which the dose is delivered) for a given dose and this range thus constitutes the region demarcated as high dose.

In this section we describe the methods employed in estimating genetic risk to low doses of x- or γ-rays. Dominant risks are derived by extrapolating from known induced dominant conditions in the mouse (that is, skeletal or cataract) to humans using several assumptions described below. The specific locus recessive mutation rates of the mouse serve as the basis of extrapolation for X-linked mutation estimates in man. For diseases resulting from chromosome aberrations, the data of human and marmoset irradiated spermatogonia are the basis for extrapolating to chromosomally abnormal liveborn. A set of correction factors is necessary; they involve dose and dose rate, transmission component, the ratios of chromosomally imbalanced translocation to balanced chromosome products, and the expected survivability of the unbalanced translocation products as abnormally produced individuals. The fourth category of genetic disease expected among the first generation offspring is the result of aneuploidy, that is, deviations in chromosome number. Because there are no existing experimental mammalian data showing a radiation-induced contribution at low dose, it is, of course, possible that the genetic risk is zero. As a result, the doubling dose approach will be used (see next section) to provide the upper limit for this form of risk.

8.4.1 Dominant and X-linked Single-Gene Disorders

The BEIR III committee employed data unavailable to the BEIR I committee to estimate the expected increase in first generation effects from increased radiation exposure. These data involved skeletal defects which were observed in the immediate offspring of irradiated male mice (Ehling, 1965, 1966; Selby and Selby, 1977). More recently Ehling's group (Ehling *et al.*, 1982) has shown that eye cataracts are inherited in the same dominant fashion. Based upon estimates of the proportion of all dominant diseases represented by such skeletal and eye disorders and extrapolating from high dose exposures, the BEIR III committee estimated that a dose of 0.01 Gy to each of the two parents would result in an additional 5 to 45 cases of dominant disorders per 10^6 liveborn after paternal exposure of spermatogonial cells (these are the important precursor cells to sperm and are present throughout reproductive life, as a result, mutations accumulate and, except for those eliminated by cell death, are transmitted by the sperm to later generations). Estimates of the maternal contribution to this class of mutation based on female mouse data are, however, fraught with considerable uncertainty. The BEIR III committee estimated that the female contribution to induced recessive disease would be at most 44% that of the male for the appropriate oocyte cells of interest; the committee simply assumed this figure for dominant mutations as well. We believe that the present scientific evidence indicates that the mouse female may not be an adequate surrogate for the human female and we have based our calculations on the assumption that human female germ cells are approximately equivalent in sensitivity to those of the male (see Appendix 3B). Thus the risk of dominant disorders per Gy of chronic exposure of both parents will be taken to range from 1000 to 9000 cases per million liveborn. This range of values was assumed by the BEIR III committee to include that fraction of multifactorial diseases that are manifest in the first generation offspring. For a single point estimate the geometric mean of 30 cases per 10^4 can be taken. The male and female gametic rates are both 15×10^{-4}/Gy (central estimate; see Appendix 3D for the range). Essentially the method of calculation of risk can be summarized in the following equation:

(3.1)

	(A)		(B)		(C)		(D)		(E)
RISK =	Induction rate of skeletal mutants	×	Correction for dose, dose rate, and fractionation	×	Correction for total dominant diseases	×	Correction for seriousness	×	Correction for sex

where $(A) = 37/2646$; $(B) = 1/6 \times 1/3 \times 1/1.9$; $(C) = 5 - 15$; $(D) = 0.25 - 0.75$; and $(E) = 1$. In Section 3.5 we provide a more general statement of the equation to account for our best estimate of the dose relationship for acute and chronic exposures.

The above more direct method (based as it is on induced dominant mutations) for estimating single gene dominant first generation effects contrasts with that used by the BEIR I committee which used mouse induced rates and human spontaneous rates to estimate relative mutation risk and estimated, first, the equilibrium level of mutation, and, then, determined from that the first generation effect. At the time of the 1972 report, the BEIR I committee lacked convincing evidence for an induced dominant phenotype that could be used for estimation of risk. The BEIR III committee also used the doubling dose range (0.5-2.5 Gy) to estimate the equilibrium level of mutation. A word of caution about the doubling dose methodology should be interjected here. Since in BEIR III the doubling dose is primarily calculated from the spontaneous and induced *recessive* mutation rates from the mouse and then applied to *dominant* mutations or other endpoints, it may not be the most accurate indicator of risk. Nevertheless, it is the only method available when data on induced mutations in the first generation are unavailable. We will use an intermediate value of 1.0 Gy (as did the authors of UNSCEAR, 1977, 1982) as a point estimate of the doubling dose for chronic exposure and 0.5 Gy as the doubling dose for acute, high exposure to account for the dose-rate effect at 1 Gy acute irradiation (see, however, Appendix 3C). The BEIR III range of values can be employed to provide an upper and lower estimate of risk. For dominant disorders, then, the effect of 1 Gy per generation (equilibrium value) or the cumulative effect of a single dose of 1 Gy on all subsequent generations can be calculated by multiplying the current incidence of dominant disorders per 10^4 and the inverse of the doubling dose, the relative mutation risk, (1/1), and the mutation component (1). This method yields an estimate of 10,000 (with a range of 4,000 to 20,000) additional cases per 10^6 liveborn per 1 Gy of parental exposure. The mutation component is the proportion of the incidence or impact of a disease that is caused by recurrent mutation. About five generations were estimated as the equilibrium period for dominant diseases by the BEIR I committee. Thus, 1/5 of the equilibrium number of cases, that is, 2,000 (range 800 to 4,000), would be the first generation point estimate, in contrast with the 3,000 cases calculated by the direct approach. In Appendix 3C we provide a discussion of the doubling dose estimates developed by Schull *et al.* (1981a,b) from the Japanese data and our reasons for not using them in our calculations.

X-linked recessive diseases are primarily diseases that affect males. The male mouse recessive specific locus mutation rates have been obtained under a variety of low dose-rate radiation regimens. We shall assume that the sensitivity is the same in both sexes and that germinal selection against X-linked recessive lethals in spermatogonial cells is unlikely to impact substantially on the male rate (in Drosophila about 50% of the X-linked lethals

induced in spermatogonia are cell inviable). At low dose rates the mouse mutation rate per locus is 7.2×10^{-6} per Gy. For humans the exact number of X-linked genes is unknown, although McKusick's compendium (1983) lists 115 X-linked diseases and an almost equivalent number of diseases of less certain origin. Thus, over 200 X-linked traits are known and the number will undoubtedly increase. We have therefore chosen to multiply the mouse rate by 250 to directly obtain an X-chromosome gametic rate of 1.8×10^{-3} mutations induced per male or female gamete per Gy (central estimate; see Appendix 3D for the range). As was done by the BEIR I committee, we assumed an average persistence time of six generations for newly introduced X-linked mutations.

3.4.2 Multifactorial Diseases

Since no direct induction rates are known for these disorders, an estimation of the equilibrium value for multifactorial diseases requires a doubling dose approach:

$$\text{Risk} = \textit{incidence} \times \textit{relative mutation risk} \times \textit{mutational component.} \qquad (3.2)$$

The mutational component was estimated to range between 1/20 and 1/2 for these diseases. Thus at equilibrium (based on a highly uncertain and conservative estimate of at least 10 generations), we can calculate that $90{,}000 \times 1 \times 1/20$ to $1/2 = 4{,}500$ to 45,000 additional cases per million per Gy will result. The point estimate based on the geometric mean is 14,200 cases per million liveborn/Gy, which provides a gametic rate, at equilibrium, for males or females of 71×10^{-4}/Gy (central estimate). The same number of cases is expected through all time for a 1 Gy parental exposure in a single generation. An even wider spread of values, 1,800 to 90,000, is obtained when the range of doubling doses is introduced. The BEIR III genetics subcommittee stated that the first generation dominant effects subsumed the multifactorial diseases.

Because of the very considerable uncertainties in attempting to estimate induced frequencies of irregularly inherited diseases on a generation-by-generation basis, we have concluded that it would be unwise to go beyond the present "state of the art" calculations and thus we will refrain from making estimates for the accident scenarios to be discussed later. We do not know the real persistence time over which such mutations will be manifest nor do we know the mutation component and thus are unable to predict with any sense of accuracy the number of cases per generation, nor do we know the nature of the multigenic interactions with themselves or with different environmental conditions.

3.4.3 Chromosome Aberrations

3.4.3.1 Translocations

The BEIR III committee employed the data of Brewen *et al.* (1975) on human and marmoset x-ray-induced translocations in spermatogonia as the basis for its estimates. The rate per Gy of balanced translocations was 7.4×10^{-2}. After correction for dose and dose rate (0.1-0.5), transmission fraction (0.25), the ratio of unbalanced to balanced (2), and the estimated survival of unbalanced aneuploid zygotes (0.05), they estimated between 100 to 1,000 cases per 10^6 liveborn would occur in the first generation from low dose-rate exposure. This compares with the estimate of 30 to 1,300 cases per 10^6 liveborn in the UNSCEAR Report (1982). Recent analysis (Trunka, personal communication) of aneuploid offspring

produced by translocation carrier parents suggests that the 5% estimate used in the BEIR Reports (1972, 1980) may be low by a factor of 2. This would change the BEIR III Report estimate by broadening the range to 100 to 2,000 cases per million liveborn per Gy delivered at low dose rates. Again, a geometric mean estimate of 500 cases might be most appropriate with the upper bound taken as 2,000.

In order to provide a single central risk estimate for induced translocations and the unbalanced segregation products, some of which produce viable and seriously affected liveborn, we suggest the following analysis. It is based directly on the induced frequency of translocations observed in primary spermatocytes, derived from irradiated spermatogonial cells of primates, that is, human and marmoset. The observed rate was approximately 7.4×10^{-2} balanced translocations per Gy from acutely delivered x-ray doses (0.25-1.00 Gy). At higher doses the response appears to saturate in the marmoset. We corrected this rate for low dose rate x-ray by a factor of 2 (see Section 3.5.1), and for γ-ray RBE by a factor 2.5 (see NCRP, 1980),[3] and derived an estimate of induction of balanced translocations in spermatogonia of

$$7.4 \times 10^{-2} \times (1/2) \times (1/2.5) = 1.48 \times 10^{-2}/Gy \tag{3.3}$$

It is further assumed that after meiotic segregation of such translocations in males, 1/4 of the gametes on the average will contain a balanced translocation, 1/2 will transmit unbalanced translocation products, with about 1/10 of these possibly surviving. The remaining 1/4 will contain normal chromosomes. Thus the frequency of translocation heterozygotes (balanced translocations) progeny should be approximately:

$$1.48 \times 10^{-2} \times 1/4 = 3.7 \times 10^{-3}/Gy \quad (\textit{Balanced Translocations}) \tag{3.4}$$

Not all of these would be expected to be benign, since complete sterility has been reported in some human male translocation heterozygotes.

The frequency from paternal exposure of unbalanced translocation heterozygotes that could survive would be:

$$1.48 \times 10^{-2} \times (1/2) \times (1/10) = 7.4 \times 10^{-4}/Gy \quad (\textit{Unbalanced Translocations}) \tag{3.5}$$

For irradiated human females there are no data. We have therefore chosen to assume (as did the BEIR III committee) the same induction rate as in the male, 1.48×10^{-2}. Since most translocations in oocytes are expected to be of a chromatid rather than of a chromosome type, the segregation products are expected to be different than the male (UNSCEAR, 1982).[4] Only 1/16 of the eggs will carry a balanced heterozygous translocation. Thus the recovery frequency would be:

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[3] See NCRP 1980 for RBE of γ-rays vs 250 kVp x-rays.

[4] The oocyte will contain the reciprocal translocation distributed between two tetrads of chromatids. The probability of recovering a balanced translocation is $1/4 \times 1/4$ or 1/16, the probability of recovering normal products is $3/4 \times 3/4$ or 9/16, and the probability of recovering an unbalanced product is $2 \times 3/4 \times 1/4$ or 6/16.

$$1.48 \times 10^{-2} \times (1/16) = 9.25 \times 10^{-4}/Gy \quad (\textit{Balanced Translocations}) \tag{3.6}$$

Six-sixteenths of the gametes will contain unbalanced translocation products, again 1/10 of these would be expected to be viable; therefore the recovery frequency after maternal exposure would be:

$$1.48 \times 10^{-2} \times (6/16) \times (1/10) = 5.6 \times 10^{-4}/Gy \quad (\textit{Unbalanced Translocations}) \tag{3.7}$$

Thus we would expect about 1,300 cases of viable unbalanced disease cases per million per Gy when both parents are exposed.

It should be noted that balanced translocation heterozygous children would be expected to transmit the following ratio of gametes to their offspring: 1/4 balanced translocations, 1/2 unbalanced and 1/4 normal.

3.4.3.2 Aneuploidy

The 1980 BEIR III committee refrained from developing a risk estimate for numerical chromosome aneuploidy (nondisjunction) because mouse tests were negative and because human studies were equivocal. An International Commission on Radiological Protection Task Group (Oftedal and Searle, 1980) used the doubling dose approach to derive such a risk estimate. Using the spontaneous human incidence of numerical aneuploidy, 0.005 times the relative mutation risk, 1, times a 0.6 correction factor for differential sex transmission, yields an upper bound of 3,000 cases per million per Gy (30/rad).[5] In the absence of experimental mammalian data, the lower bound could be zero risk. Again, if a single point estimate within this range is desired, 500 cases/10^6 gametes/Gy. We have used one case as the lower bound (which is within the Poisson limits of 0) and our calculation was as follows for 1 rad:

$$\sqrt{1} \times 30 = 5 \; cases/rad \times 100 \; rad/Gy = 500 \; cases/Gy$$

We will also assume that the yield of these aberrations follows a linear relationship throughout the anticipated dose-response curve.

3.4.4 Summary of Low-Dose Risk Estimates

In summary, first generation effects per Gy of exposure (delivered at low dose rate) would be expected to produce 3,000 cases of dominant gene and multifactorial disorders (range, 1,000 to 9,000), 900 cases of X-linked disorders adjusted for sex-ratio (range, 0 to 3600) and 2,300 cases of chromosomally abnormal offspring (range, 400 to 11,000) resulting from translocations and nondisjunction per million liveborn. (See Appendix 3D for a detailed presentation of ranges.)

In Table 3.1 we presented for comparative purposes the central estimates of induced genetic diseases relative to the normal incidence for this study and that of the BEIR III Report (NAS, 1980). For this table, the 1978 demographic data of one million persons of all ages were used to predict the first generation offspring population size. Such a population

[5] The ICRP Task Group assumed the relative mutation risk for aneuploidy was the same as that for mutation (1 Gy).

would be expected to produce about 16,000 births per year or about 480,000 births over the first generation. Therefore, all of the cases of induced genetic disease for each class that were calculated in the previous sections on the basis of 1,000,000 liveborn have been corrected for this birth rate, that is, multiplied by 0.48. Table 3.1 presents the data on the basis of a 0.01-Gy (1-rad) exposure rather than that calculated at 1 Gy and, *assuming stable population size,* estimates the number of cases of genetic disease expected over all time (in addition to first generation predictions) from a single 0.01-Gy exposure.

For second generation effects, the dominant and X-linked disorders will decrease by about 20% and the unbalanced chromosome anomalies by about 33%. Chromosome anomalies are expected to have a three generation average persistence, thus the reduction by 33%. Finally the chromosome aneuploids are not fertile and would not be observed in subsequent generations unless as a result of an unbalanced translocation. A graphic illustration of the dynamics of the various classes of genetic disease following a dose of 0.01 Gy (1 rad) is shown in Figure 3.1.

3.5 Radiation Risk Estimates: High Doses Delivered at High Dose Rates

The dose-response curve for gross chromosomal aberration induction rises faster than linearly after high doses of low-LET X or γ irradiation delivered at high dose rates. A linear-quadratic, $Y = \alpha d + \beta d^2$, equation can be fitted to much of the mammalian and nonmammalian experimental data when a wide range of doses have been studied. We suggest the use of the same relationship for those endpoints conventionally classified as gene mutations when induced by high energy X or γ radiation. In *Drosophila* oogonial mutation studies and *Tradescantia* mutation experiments, where a much wider range of doses have been employed, the linear-quadratic equation provides the best fit to the data and a linear response is not applicable. In mouse oocyte studies up to 6 Gy, again the linear-quadratic response fits the data extremely well and the linear response provides a poor fit. In mouse spermatogonial studies at acute doses (3 to 10 Gy), a humped shaped curve has been observed. These limited doses (3 points) do not provide an adequate range to establish a fit over the range of interest. Moreover the dose response for protracted irradiation is linear and significantly below the response obtained at acute doses, suggesting a dose squared contribution at high acute doses (see NCRP 1980 for details on the above points). Finally where extensive studies have been carried out on radiation-induced specific locus mutations in mammalian somatic cells (UNSCEAR, 1982) on three different loci (ouabain resistance, HGPRT and LDH-A mutations), the data all indicate that these mutations are predominantly the result of deletions (or other types of chromosome aberrations) as opposed to single nucleotide base substitutions. Thus the chromosome breakage nature of the mutations indicates production of either two breaks induced by a single track event or by interaction of two independent tracks.

3.5.1 Dominant and X-linked Single-Gene Disorders

In order to develop a linear-quadratic equation, $Y = \alpha d + \beta d^2$, to incorporate the expected yield of dominant mutations for both low dose-rate and high dose and high dose-rate exposures to low-LET radiation, we have made the following assumptions:

(1) The dose-frequency response relationship for dominant mutations will parallel that obtained from specific locus mutations but the coefficients will be different. The estimated coefficients, α_r and β_r, for specific locus *recessive* mutations in the mouse are

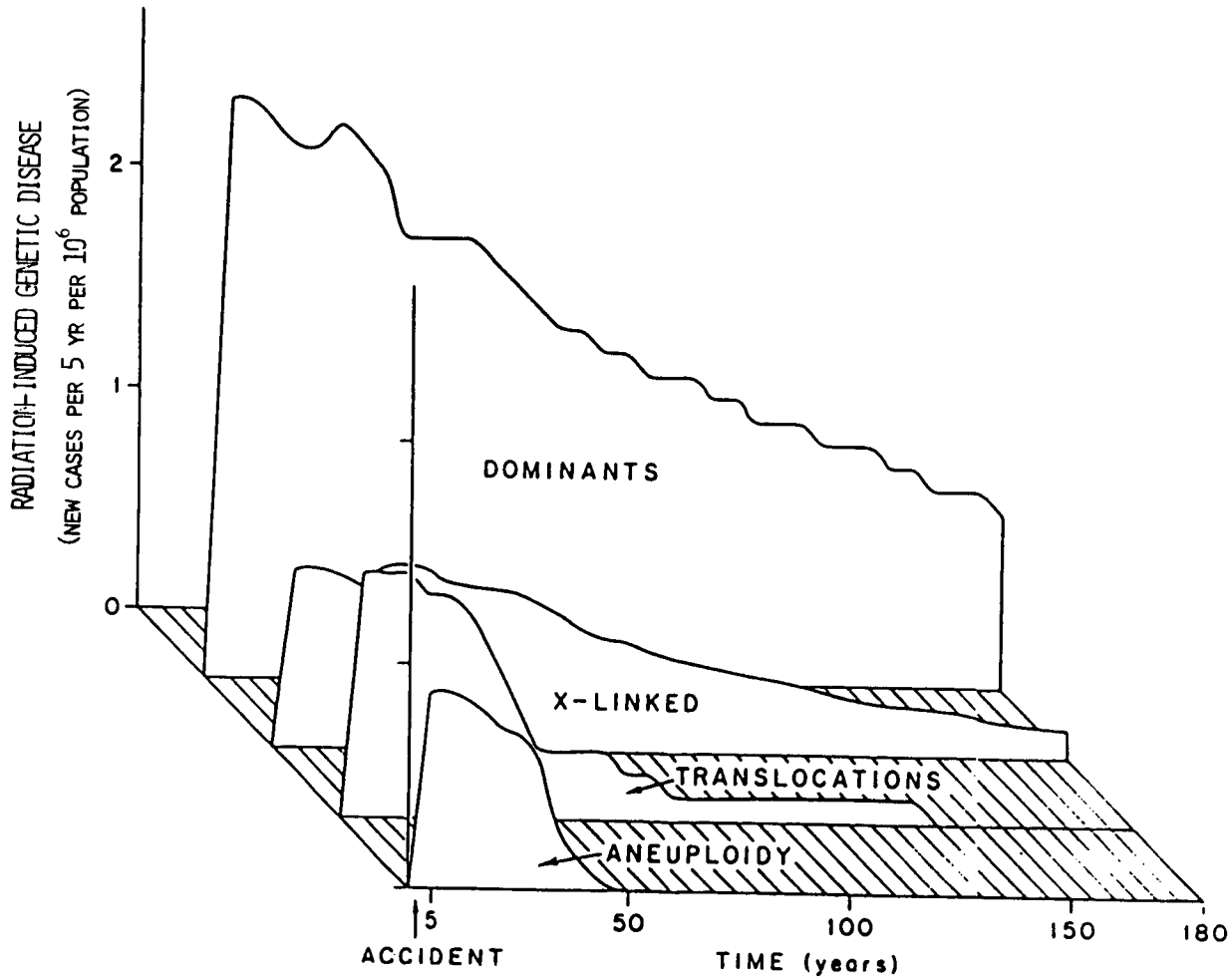

Figure 3.1 **Incidence of radiation-induced genetic disorders. Effect of** a uniform gonadal dose of 0.01 Gy, delivered acutely.

0.7×10^{-7} and 0.7×10^{-9} per locus per rad, respectively (Abrahamson & Wolff, 1976; NCRP, 1980; Denniston, 1982). It is important to recognize that the α/β values for specific locus mutations is 100 rad or 1 Gy, which in fact means that at this dose the 1 track contribution is equal to the 2 track radiation concentration, to the genetic target. We will assume the same α/β ratio for dominant effects.

(2) The estimated skeletal defects yield per Gy (BEIR, 1980) determines that $\alpha_D/\alpha_r \approx 90$ (where α_D is the linear coefficient of dominant disorders), suggesting that the combined target size for skeletal defects is about 90 times larger than that for a single locus.

(3) Thus for dominant mutations we will assume that the equation $Y = (6.5 \times 10^{-4})d + (6.5 \times 10^{-4})\ d^2$ estimates the expected yield of dominant skeletal mutations for acute exposure where d is the dose in Gy.

We then derived, as discussed earlier, the total induced rate for all dominant disorders to be 1.5×10^{-3} per gamete per Gy for low doses. Thus, the equation we shall employ for high dose exposures is:

$$Y = (1.5 \times 10^{-3})d + (1.5 \times 10^{-3})d^2 \tag{3.8}$$

per male or female gamete. If the dose is received in a chronic fashion, the β coefficient becomes zero and the yield is αd.

For the yield of X-linked recessive mutations we used the mouse specific locus rate values multiplied by 250 to adjust for the expected number of human X-linked genes:

$$Y = 1.8 \times 10^{-3}d + 1.8 \times 10^{-3}d^2 \tag{3.9}$$

per male or female gamete.

3.5.2 Chromosome Aberrations

3.5.2.1 Translocations

We recognize that there may well be a saturation effect at high doses for *transmitted* chromosome aberrations induced by high doses of acute low-LET irradiation, leading to fewer cases than predicted. Nevertheless we have chosen to use for γ rays the linear-quadratic equation for acutely received doses up to 2 Gy to which the modifications discussed earlier would be appended, namely:

$$Y = 1.48 \times 10^{-2}d + 1.48 \times 10^{-2}d^2 \tag{3.10}$$

Again, if the dose is delivered chronically, the β coefficient becomes zero and the yield is αd.

Two general points concerning the linear-quadratic dose-response curve should be considered. First, the equation is appropriate for acute doses up to approximately 5 Gy. Above this dose, and possibly at doses lower than this in primates, there is accumulating experimental evidence that the curve begins to saturate because of cell killing, resulting from inviable chromosome aberrations, which selectively eliminates the mutant cell population. Complete sterility is the ultimate end point of this high acute dose phenomenon. Second, the quadratic

term is dependent on the dose rate. Lea (1955) introduced the modification, G, which corrects for the time (usually in the range of hours) available for the interaction of chromosome breaks produced by separate ionization tracks in metabolically active cells. For purposes of this report, we shall assume G = 1 if the acute high dose exposure was received within a 24-hr interval, that is, we will assume complete interaction of independently produced breaks over this time period.

3.5.2.2 Aneuploidy

For chromosome aneuploidy, there is as yet no dose-response relationship that has been established in mammalian tests. We therefore recommend that 500 cases per million per Gy be used as the coefficient of dose per gamete:

$$Y_{aneuploids} = 5.0 \times 10^{-4} d \tag{3.11}$$

3.6 Estimated Impact of Genetic Disease (Years of Life Lost)

Tables 46-49 in the UNSCEAR Report (1982) introduced estimates of years of life lost for major human genetic disorders. These tables are reproduced in Appendix 3F. These estimates are weighted, and are determined by taking the frequency of the specific types of genetic diseases and multiplying by the estimated number of years of life lost per disease entity. In addition, subjective estimates of the years of impaired life and the degree of impairment were also developed. The product of these weighted values yields the *effective years* of life lost. The two components, years of life lost and effective years of life lost, have their counterparts in fatal and nonfatal cancers, and thus provide some common ground for combining the impacts of the two major radiation-induced events. While it should be understood that considerable subjectivity is introduced into these estimates, we expect that future research will narrow the range of uncertainty. Dominant disorders were estimated to cause an average of 13 years of life shortening and an additional 8 effective years of life lost. The additional 8 years of life lost arrive from 25 years of impaired life at 33% impairment. X-linked disorders were estimated to cause 40 years of impaired life at about 40% impairment, that is 16 effective years of life lost in addition to 28 years of life shortening. For our purposes, unbalanced translocation disorders shall be equivalent to 70 years of life lost and 46 years lost as an average for all aneuploids. We assume a 70 year average life expectancy for normal individuals.

Combining these values with those presented in the previous section leads to the following estimates of genetic impact per 0.01 Gy of parental exposures: For dominants, about 630 years of life lost (30×21) per million liveborn; for X-linked about 400 years (9×44); and for all chromosome anomalies about 1,370 years ($10 \times 46 + 13 \times 70$); for a total of 2,400 years of life lost per million liveborn who would otherwise have anticipated 70 million years of life in the first generation. The UNSCEAR estimate was 30 years of life lost for the irregularly inherited disorders and 20 years of impaired life, but the UNSCEAR Report (1982) provided no estimate of the degree of impairment. It is assumed for purposes of the present report that a reasonable range of values would be from 15% to 30%. Thus, for our estimates, the total number of effective years of lost life is found by multiplying 33 to 36 years per case times 68, the number of cases throughout all times per 0.01 Gy of parental exposure. The result is approximately 2350 years. We have adjusted the expected 145 cases per million

offspring to the 1978 vital statistics by applying a factor of 0.48. This yields 145 $\times$ 0.48 or 68 cases throughout all times. These estimates scaled to the 1978 vital statistics are presented in Table 3.2. The resulting estimates can be compared with those resulting from the normal incidence of genetic disease.

3.7 Accident Scenarios

To illustrate how our approach should be applied, we have projected the increase in genetic diseases that would be expected to occur following scenarios involving two hypothetical patterns of dose. The projections have been carried out for 150 years following each scenario. During this time period most of the single-gene and chromosome disorders would be manifest.

Scenario 1 involves an accumulated dose of approximately 0.1 Gy received chronically over approximately fifty years, 0.04 Gy being received in the first five year period. Scenario 2 assumes that the population at risk received an acute dose of 2 Gy (that is, within about a 24 hour period) immediately following an accident. In both scenarios we follow the rise in dominant, X-linked and chromosomal anomalies over continuing five year periods. Tables 3.3 and 3.4 and Figures 3.2 and 3.3 provide the summarized data for these two scenarios over the first five generations. In Appendix 3G we provide a description of the demographic assumptions and programs utilized as well as a sample program output. [Copies of programs for the modelled genetic effects are available upon request.]

3.8 Review of Hiroshima-Nagasaki Genetic Effects

Schull *et al.* (1981a,b) have reviewed the long-term ongoing analysis of the genetic effects in children of the atomic bomb survivors of Hiroshima-Nagasaki. In the tables of their paper they provide a distribution of fathers' and mothers' doses and the distribution of normal and affected progeny for the dose ranges involved. While we are aware that the dosimetry is in the process of revision, the absorbed doses (e.g., Gy) employed are less subjective than dose equivalents (e.g., Sv) since they involve no assumptions about RBE nor dose-rate reduction responses. By using the linear-quadratic equations for the induction of gene mutations and chromosome aberrations, which were developed independently of the Japanese data, it is possible to predict for each exposure sample the expected number of cases (Table 3.5). We have used an average dose for each exposure group, that is 0.05 Gy (0.01-0.09 Gy parents groups), 0.295 Gy (0.10-0.49 Gy groups), 0.745 Gy (0.50-0.99 Gy groups) and 2.00 Gy ($\geq$ 1.00 Gy groups) and introduced these values into the equations presented in Section 3.5 to project the number of cases of each genetic event relative to the child sample size in each of the 32 sectors of exposure in the Schull *et al.* matrix.

Among the 16,713 children born to parents, one or both of whom were exposed, we conclude that there should have been about 50 total cases of genetic defects distributed as follows: 24 dominant, 5 X-linked, 4 aneuploid and 15 unbalanced translocations (early deaths) plus 55 cases of balanced translocation (detectable in otherwise normal individuals). In addition, the lower limit prediction is about 8 additional cases of genetic defects plus 6 individuals with balanced translocations and the upper limit prediction is approximately 170 additional cases of genetic defects plus 137 individuals with balanced translocations. It should be obvious that the central estimate prediction of cases should lead to a statistically insignificant, that is, undetectable increase in genetic disorders among the 16,713 progeny of irradiated

Table 3.2 Estimated Numbers of Years of Lost Life In a Population of One Million Associated With Naturally Occurring and Radiation-Induced Genetic Disorders, Derived from Table 5.1[a]

Type of Disorder	Years of Life Lost Due to Normal Incidence[b]		Years of Life Lost Due to Radiation (0.01 Gy)[c]		
	Per Year	Per 30 Years	Per Year	Per 30 Years	Sum for all Generations
Single-gene[d]	3,600	108,000			
Autosomal Dominant			10	300	1,510
X-Linked[e]			7	220	1,320
Irregularly[f] Inherited	52,700	1,580,000	-	-	2,350
Chromosome[g] Aberrations					
Aneuploidy	3,700	110,400	6	185	230
Unbalanced Translocations	1,100	32,200	14	420	700
TOTALS	61,100	1,830,000	40	1,100	6,100

[a] Based primarily on UNSCEAR (1982) estimates. The numbers have been rounded off to avoid perception of false precision.

[b] For a total population of 10^6 (16,000 live births per year).

[c] Effect of 0.01 Gy dose to each of 10^6 persons. Calculated using 1978 demography, which assumes a projected birthrate (births/year) of 16,000 for each of the first 30 years, 15,600 for each of the years 30 through 59, and 15,000 for years 60 through 89.

[d] Dominants estimate: 13 years lost + 25 years impaired x 33% impairment = 21.

[e] Sex-linked estimate: 28 years lost + 40 years impaired life x 40% impairment = 44.

[f] Irregularly inherited disorders estimate: 30 years lost + 20 years impaired x 25 % impairment = 35.

[g] Chromosomal aberration estimate: 46 years lost (weighted average for X and autosome aneuploidy, from UNSCEAR 1982, Table 49; unbalanced translocations, 70 years life lost.

[h] Totals rounded off.

Table 3.3 Estimated Radiation-Induced Genetic Effects, Scenario 1 (Chronic Exposure)[a,d]

Type of Disorder	Total Cumulative Cases: Years Since Accident				
	30[c]	60[c]	90[c]	120[c]	150[c]
Dominant Central Estimates	110	240	360	440	510
X-Linked Central Estimates[b]	35	80	120	140	160
Aneuploidy	30	50	50	50	50
Unbalanced Translocations	45	80	100	100	105
Cumulative Mutant Totals	220	456	642	730	825
Cumulative Births	490,000	958,000	1,410,000	1,850,000	2,270,000

[a]Dose accumulated in 5 year intervals:
1) 0.04 Gy; 2) 0.01 Gy; 3) 0.01 Gy; 4) 0.01 Gy; 5) 0.0075 Gy;
6) 0.0075 Gy; 7) 0.0025 Gy; 8) 0.0025 Gy; 9) 0.0025 Gy; 10) 0.0025 Gy.

[b]Central estimates: includes 70% viability of induced mutants in each generation.

[c]Demography: 1978 projection (adjusted to produce stable population size)

Time Period (yr)	Projected Birthrate (Births/yr)
0-29	16,000
30-59	15,600
60-89	15,000
90-119	14,700
120-149	14,000

[d]Results rounded to three significant figures. Three "significant" figures are provided to permit derivative calculations and to facilitate verification of our results. They are not intended to imply that risks can be projected this precisely.

Table 3.4 Estimated Radiation-Induced Genetic Effects, Scenario 2 (Acute Exposure)[a,d]

Type of Disorder	Total Cumulative Cases: Years Since Accident				
	30[c]	60[c]	90[c]	120[c]	150[c]
Dominant Central Estimates[b]	8,960	16,330	22,180	26,850	30,570
X-Linked Central Estimates	2,890	5,560	7,400	8,680	9,570
Aneuploidy	920	1,010	1,010	1,010	1,010
Unbalanced Translocations	3,640	5,010	5,580	5,830	5,930
Cumulative Mutant Totals	16,500	28,200	37,900	42,370	47,080
Cumulative Births	489,000	954,000	1,400,000	1,850,000	2,270,000

[a]Dose: 2 Gy in first interval, none in the following intervals.

[b]Central estimates: includes 70% viability of induced mutants in each generation.

[c]Demography: 1978 projection (adjusted to produce stable population size)

Time Period (yr)	Projected Birthrate (Births/yr)
0-29	16,000
30-59	15,600
60-89	15,000
90-119	14,700
120-149	14,000

[d]Results rounded to three significant figures. Three "significant" figures are provided to permit derivative calculations and to facilitate verification of our results. They are not intended to imply that risks can be projected this precisely.

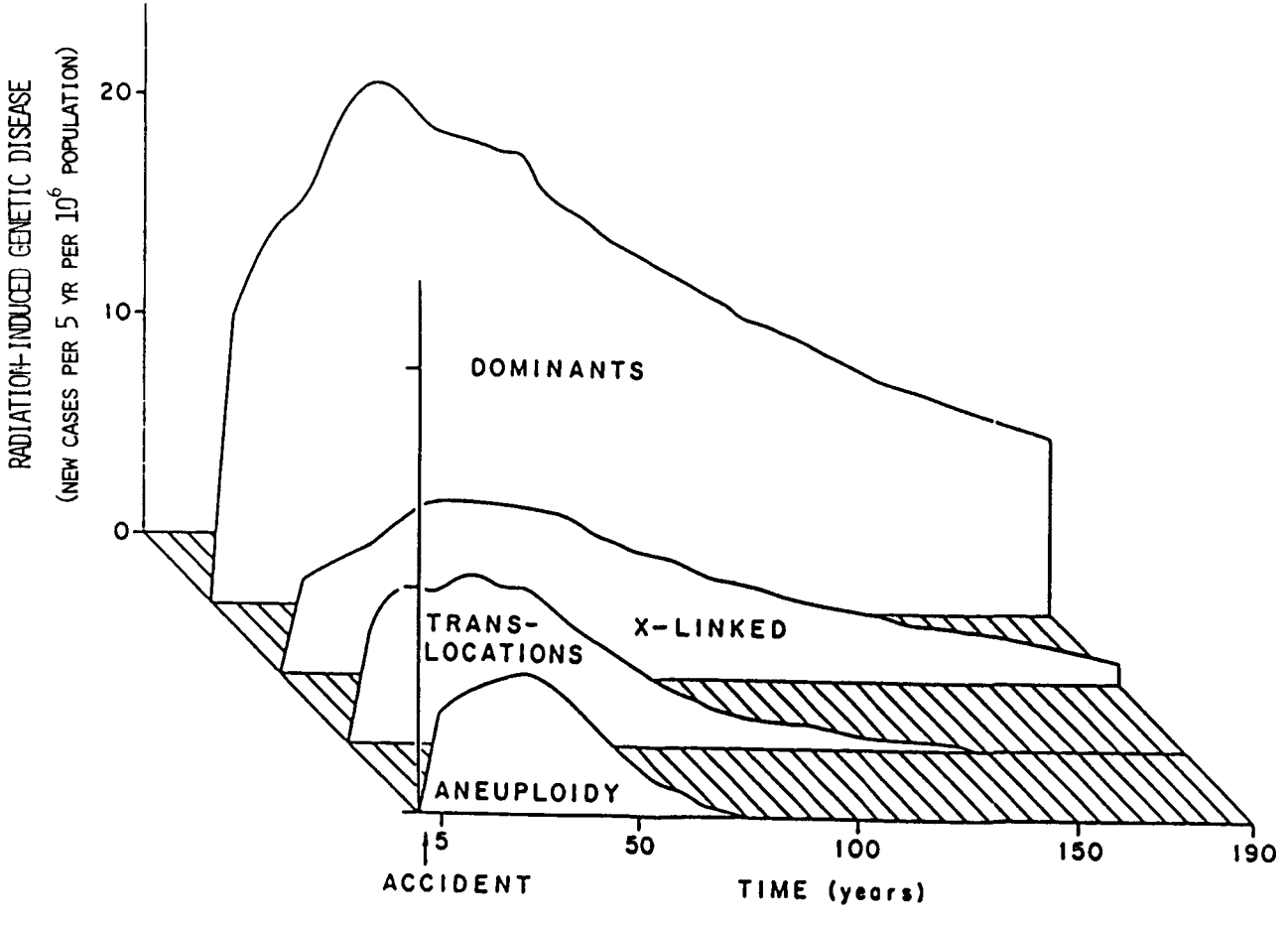

Figure 3.2 **Incidence of radiation-induced genetic disorders. Effect of** a uniform gonadal dose of 0.10 Gy, delivered chronically.

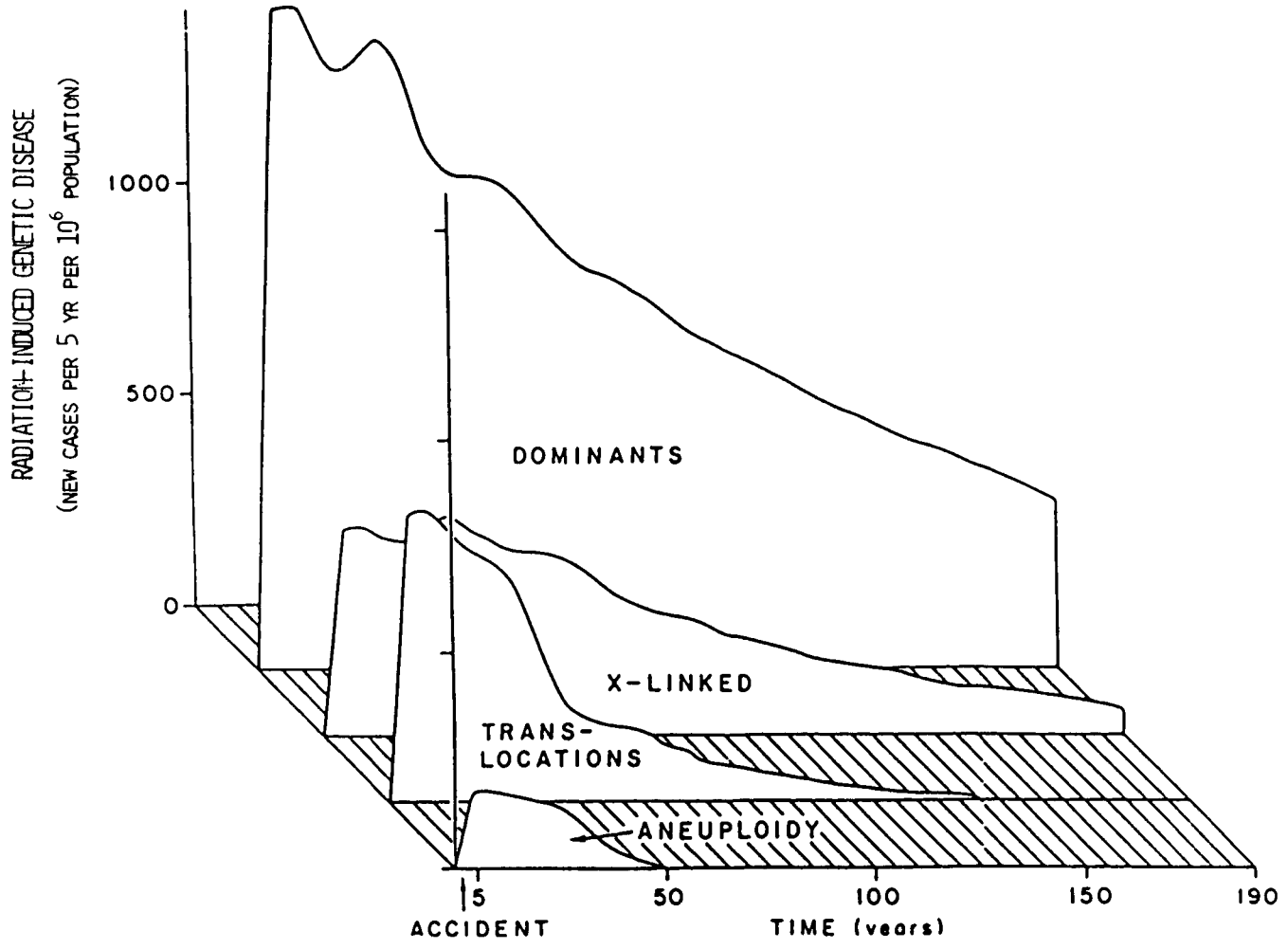

Figure 3.3 **Incidence of radiation-induced genetic disorders. Effect of** a uniform gonadal dose of 2.00 Gy, delivered acutely.

Table 3.5 Central Estimate of First Generation Cases of Genetic Disease in 16,713 Offspring of Japanese A-Bomb Survivors[a]

Effect	Estimated Number of Cases by Average Parental Dose[b] (Gy)				Total Estimated Number of Cases	Father Exposure Only[e]
	0.034	0.218	0.706	2.435		
Genetic Disease						
Dominants	0.5	2.3	4.6	26.5	33.8	(18)
X-Linked[c]	0.2	0.5	0.8	3.5	5.0	(0)
Aneuploid	0.2	0.6	0.9	2.6	4.3	(2)
Unbalanced Translocations	0.2	1.0	1.9	11.8	14.9	(8.5)
Total For All Diseases	1.1	4.4	2	44.4	58.0[f]	(29)
Balanced Translocations[d]	0.6	2.9	6.3	45.5	55.0[g]	(46)

[a]Based on linear-quadratic models with central estimates of model parameters. Based on followup to 1975.

[b]Kato and Schull (1982).

[c]Based on number of sons produced by exposed mothers only.

[d]Signal phenotype.

[e]Numbers in parentheses designate central estimate if mothers germ cells were "insensitive" to irradiation or were selectively eliminated by irradiation.

[f]Our models would predict a lower bound estimate of 3 cases and an upper bound estimate of 136 cases.

[g]Our models would predict a lower bound estimate of 3 cases and an upper bound estimate of 63 cases.

parents. For example there were 1,040 deaths in this group of 16,713 progeny up to the age of 17 (6.22%). In the unexposed groups there were 2,191 deaths of 33,976 progeny produced (6.45%), and the two frequencies are not significantly different, nor would they have been even if 50 additional cases were added to the exposed group. Finally we note that our predictions of the number of balanced translocation progeny can be used to provide a test of the sensitivity of the rearrangement models employed because such cytological tests are being carried out on the progeny and this class of events (balanced translocation) should show less selective disadvantage than the other categories described. Moreover the finding of induced balanced translocations in progeny of irradiated mothers would provide critical evidence that the human immature oocyte is mutable by radiation (unlike the mouse oocyte). In conclusion, we reiterate that our calculations provide a not unreasonable estimate of the genetic effects observed in Japan.

3.9 Computational Shortcuts (First Generation Effects)

It follows from our earlier discussion that, within the linear range of the dose-response curve, it is the collective dose to the population that will determine the genetic risk estimation. That is, a dose of 0.1 Gy to 100,000 people would produce the same total number of genetic disorders as 0.01 Gy to 10^6 people or 0.2 Gy to 50,000 people. This is equivalent to saying that, as long as all individual doses are within the linear portion of the dose-response curve, it is the average dose to the population that will determine the genetic risk estimate.

When the dose is received acutely at high doses (above 0.5 Gy) by different segments of the population, then the calculation requires multiplying the number of people by the linear quadratic equations for each dose segment, and summing over each segment, for example, (10,000 people $\times$ $[10^{-4}\ d_1 + 10^{-4}\ d_1^2]$ where $d_1 = 0.75$ Gy) + (5000 people $\times$ $[10^{-4}\ d_2 + 10^{-4}\ d_2^2]$ where d_2 is 1 Gy), etc.

3.10 General Summary

In this chapter we have developed a set of general risk equations to predict the yield of the major categories of genetic diseases expected to be experienced by the offspring of a radiation-exposed population. The equations are of the form Yield = $\alpha D + \beta D^2$ where α and β are the respective coefficients for dominant, X-linked and chromosome disorders, and D represents the gonadal dose received by the male and female parents, separately. In conjunction with these equations, computer models using 1978 U.S. demography (*assuming stable population size*) allow the prediction of the distribution of the cases of genetic disease through time, that is, over approximately the subsequent 150 years following a variety of different exposure patterns (chronic low dose or acute high dose). The dynamics of this distribution are presented in both tabular and graphic form.

Our analyses differ to some extent from those published by both the BEIR and UNSCEAR committees in that we have assumed an *equal sensitivity for male* and *female germ cell stages of interest* (spermatogonia and immature oocytes). We have also developed a risk estimate for X-linked disorders and aneuploids in addition to the other genetic classes conventionally discussed, namely, dominant disorders, unbalanced translocations and multifactorial diseases. The risk estimates are presented in two forms, the number of cases induced and the impact in terms of years of effective life lost; with certain reservations, the latter approach

provides a common base line to judge either other radiation-induced risk or risks incurred by other societal activities. For each risk estimate we provide both a lower and upper range of values which bound the central risk estimates.

In addition to developing a unit risk estimate (per Gy or per rad) we have attempted to predict the genetic consequences over time of two different nuclear power plant accident scenarios and examined the consistency between our model predictions and the observed rates of genetic disease in the survivors of the World War II Japanese atomic bombings.

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Appendix 3A

RESPONSE TO CRITICISMS OF THE BEIR III REPORT

Of all the criticisms of the estimates of genetic effects published in the BEIR III report, the only substantive ones recorded in the scientific literature are those of Dr. John W. Gofman (1981). Dr. Gofman's disagreements lie largely (though not entirely) in two areas: irregularly inherited diseases and chromosomal anomalies. For the irregularly inherited diseases, he disputes two factors entering into the BEIR III committee's estimations: the current incidence of genetically related ill health, and the mutational component of such diseases. With respect to current incidence, Gofman argues that the BEIR III estimates (10.7%) are "probably 3 to 5 times too low, because important diseases of adulthood with a genetic component are simply not listed by various quasi-governmental committees". The estimate of 10.7% actually comprises a substantial fraction of such diseases having a significant mutational component. In addition, diseases occurring later in life generally appear to have a smaller genetic component, so their incidence would be increased less by increased mutation rates. Certainly Gofman's upper limit guess of five times the 9% actually observed up to age 21 seems unwarranted by the existing data.

With respect to the mutational component of such diseases, Gofman argues that the estimate of 5-50% adopted by the BEIR III Committee or of 5% adopted by the authors of the UNSCEAR reports are the product of "sheer, unsupported speculation," and adopts a value of 100% in his own calculations. Such a value is incompatible with basic mendelian genetics, however, 100% is the value for the *regularly* inherited diseases, and the value for irregularly inherited disease must by definition be less. We believe values even as high as 50%, the BEIR III Committee's upper bound, are in fact the upper bound for the mutational component of all genetic diseases, of which regularly inherited diseases are only a fraction (Crow and Denniston, 1981). Finally, on this point, one would expect 100% concordance between identical twins for these diseases; this is not observed.

Gofman's arguments regarding chromosomal anomalies involve three separate types: deletions, translocations and nondisjunction. He argues that most deletions are too small to be detected by conventional cytogenetic techniques, and "far more important than is commonly recognized". This ignores completely the fact that estimates of doubling doses are based mainly upon mouse specific locus mutation data, and these mutations include the small deletion class. Most of the mutant alleles are homozygous lethal and a large fraction are indeed large enough to be detected cytogenetically.

The disagreement over translocations lies in Gofman's miscalculation from published studies made in males exposed at high dose rate. Gofman fails to take into account the dose rate reduction factor, the fact that the transmission of translocations in females is extremely low, and the observation that the probability of recovering an unbalanced segregation product from a translocation is only about 6% although recent unpublished data could raise this figure to about 10%. When these appropriate corrections are made, the doubling dose for translocations is about 1 Gy for low dose gamma rays, not the 0.03 Gy Dr. Gofman calculates.

Gofman's argument regarding radiation-induced chromosome 21 nondisjunction is even less acceptable. After noting the extremely equivocal evidence for any such effect at all, Gofman simply adopts a lower limit value of 0.03 Gy. This, of course, implies that *all* trisomy-21 is radiation-induced as a result of natural background radiation. This is in unacceptable conflict with the evidence.

Appendix 3B

OOCYTE MUTATIONAL SENSITIVITY

The mouse dictyate oocyte is the immature stage most similar histologically to the human immature oocyte. A human oocyte at this stage is expected to accumulate genetic damage throughout the prereproductive and reproductive years. In the mouse this stage is refractory to mutation induction by all forms of high energy radiations and has been assumed in BEIR I to imply 0 sensitivity to irradiation for women. BEIR III assumed that the female germ cell sensitivity was 44% of that of the male, maximally. Recently Dobson (1983) has shown that damage to the mouse oocyte membrane as a result of traversal by ionizing radiation causes cell death, therefore the only surviving cells are the "no-hit" and therefore nonmutated, cells. This explanation has been previously invoked in the NCRP report (1980). Unlike the immature mouse oocyte which is extraordinarily sensitive to cell killing by radiation and chemicals, the human immature oocyte appears to be quite resistant to killing by radiation, tolerating doses in the range of 6-20 Gy of highly fractionated or protracted low LET irradiation (Lushbaugh and Casarett, 1976). Since there exists no mutational response data on the human female oocyte, we recommend that it be assumed to have a risk equivalent to that of spermatogonia, because the mouse data is not an appropriate basis for extrapolation.

Appendix 3C

DOUBLING DOSE CONSIDERATIONS

3C.1 Hiroshima-Nagasaki

Schull *et al.* (1981a,b) have derived doubling dose estimates for three human genetic endpoints in the offspring of the Japanese atomic bomb survivors: untoward pregnancy outcomes, childhood deaths, and sex chromosome aneuploids. In the estimation of doubling dose, they employ a gonadal dose factor that assumes an RBE of 5 for neutrons. Since the dosimetry of the Japanese bombings is now being reviewed, particularly with respect to the existence of a neutron component, the effect of the earlier dosimetry is to yield a doubling dose which is possibly too high by a factor of 2. Schull *et al.* also apply a dose effectiveness reduction factor of 3 to estimate low dose rate, low LET effects, and they use a linear model for risk extrapolation. Introducing a dose rate reduction factor for the neutron component as appears to have been done in their calculations, is inappropriate for high LET radiation. A linear quadratic model derived from experimental data is a more accurate expression of the dose response relationship (NCRP, 1980). The dose rate reduction factor is therefore not a constant but depends on the dose and dose rate. The α/β ratio (the coefficients of dose of a known quadratic equation) from this model for mammalian genetic endpoints is 1 Gy (Abrahamson and Wolff, 1976), suggesting that the maximum dose rate reduction to be expected for doses of 100R and below is two. The bulk of the human data comes from doses estimated to be in this range with 40% of the children born to parents who were exposed in the 1-9 rad dose range. These factors, as used in Schull *et al.*, lead to an increase in the doubling dose and thus produce relative risk estimates that are probably too low. When the revised A-bomb dosimetry becomes available, the doubling dose estimates may provide values that have greater applicability.

A final point on doubling dose estimates based on the linear-quadratic equations is of particular interest. The doubling dose concept suggests that about 2,000 dominant cases will occur spontaneously each generation and asks what is required to exactly double that number; or conversely what is the "relative mutation risk of a conjoint parental exposure of 1 rem (.01 Gy)" [BEIR 1972, 1980]. Assuming our central estimate of risk of dominant mutations for conjoint parental exposure is $30 \times 10^{-4}\ d + 30 \times 10^{-4}\ d^2 = 2{,}000$ cases, then an *acute* dose of 0.47 Gy is the doubling dose. For *chronic* exposure the β coefficient is zero and the doubling dose becomes 0.7 Gy. The range for the acute d value is 0.19 to 1.6 Gy, and for the chronic value it is 0.22 to 4.0 Gy.

3C.2 Recessive Mutation Disease

The following calculations will provide an approximate estimate of the induced recessive disease burden through all time. Recall that the mean persistence of a recessive mutant is some 100 times that of a dominant with the same degree of severity. Therefore the number expressed per generation is only 1/100th that of a dominant. Although we can use the doubling dose approach to calculate the total number of such cases that could occur, we are unable to describe the number of cases expected per generation.

$$\textit{Total number of recessive diseases} = \textit{Current incidence} \left(\frac{1}{\textit{Doubling dose}} \right)$$

where the *Current incidence* (corrected for 1978 vital statistics) is 1920 cases and the *Doubling dose* for chronic exposure is 1 Gy, and for acute exposure it is 0.5 Gy.

$$\textit{Total number of cases for } 0.01\ Gy = 1920 \times 0.01 \approx 20$$

$$\textit{Total number of cases for } 0.1\ Gy = 1920 \times 0.1 \approx 200$$

$$\textit{Total number of cases for } 2\ Gy = 1920 \times 4 \approx 7700$$

Appendix 3 D

Table 3.D Range of Uncertainties Associated With The Induced Mutation Rate

Type of Disorder	Estimated Induction Rate (10^{-4} Gy^{-1})		
	Central	Lower[f,g]	Upper[f,g]
Dominants[a]			
Male	15	5 (1/6)	45 (3)
Female	15	0	45
X-Linked[b]			
Male	18	7.2 (0, 1/5)	72 (4)
Female	18	0	72
Aneuploid[c]			
Male	5	0 (0)	15 (3)
Female	5	0	15
Unbalanced Translocations[d]			
Male	7.4	0.8 (1/10)	18.5 (2.5)
Female[e]	5.6	0	14.0
Irregularly Inherited Diseases at Equilibrium[a]			
Male	71	45 (1/3)	450 (6.4)
Female	71	0	450

[a] We employ the range used by the BEIR III committee for these estimates, however, for irregularly inherited traits, we assume the doubling dose is 1 Sv. BEIR assumed doubling dose .5 Sv - 2.5 Sv.

[b] Upper range based on 1000 X-chromosome genes, lower range assumes only male cells are mutated and 100 X-chromosome loci.

[c] Lower range assumes not an inducible event, upper range is based on ICRP task group calculation.

[d] Upper range assumes no dose rate reduction factors (DREF), lower range employs UNSCEAR 1982 dose rate reduction factor of 9. To estimate risk of viable unbalanced transactions in first generation correction factors from section 3.4.3.1 must be applied.

[e] Upper range assumes female cells respond like mouse maturing oocytes and are twice as sensitive as male cells for acute irradiations and no DREF, lower range assumes zero recoverability from females.

[f] The numbers in parentheses represent the factor by which the number of cases shown in the Tables 3.1-3.4 should be multiplied to obtain lower or upper estimate values.

[g] To determine range for 30-year period listed in Table 3.1, multiply values by 0.48.

Genetic Diseases of Humans (Some Cases) By Class (UNSCEAR 1977 Tables 1,2, 3,and 7 (Annex H) with modifications)

Complexly Inherited Diseases

Anencephalus
Spina bifida with hydrocephalus
Spina bifida without mention of hydrocephalus
Congenital hydrocephalus
Encephalocele
Microcephalus
Anomalies of brain
Anomalies of spinal cord
Anomalies of nervous system
Unspecified anomalies of brain, spinal cord and nervous system
Anopthalmos
Micropthalmos
Buphthalmos
Congenital cataract
Coloboma
Congenital blepharoptosis
Anomalies of eye
Unspecified anomalies of eye
Anomalies of ear causing impairment of hearing
Accessory auricle
Anomalies of ear
Unspecified anomalies of ear
Branchial cleft, cyst or fistula; preauricular sinus
Webbing of neck
Anomalies of face and neck
Unspecified anomalies of face and neck
Common truncus
Transposition of great vessels
Tetralogy of Fallot
Ventricular septal defect
Atrial septal defect
Ostium atrioventriculare commune
Anomalies of heart valves
Fibroelastosis cordis
Anomalies of heart
Unspecified anomalies of heart
Patent ductus arteriousus
Coarctation of aorta
Anomalies of aorta
Stenosis or atresia of pulmonary artery
Anomalies of great veins
Absence or hypoplasia of umbilical artery
Anomalies of peripheral vascular system
Anomalies of circulatory system
Choanal atresia
Anomalies of nose
Web of laryax
Anomalies of larynx, trachea and bronchus
Congenital cystic lung
Agenesis of lung
Anomalies of lung
Cleft palate
Cleft lip
Cleft palate with cleft lip
Anomalies of tongue
Pyloric stenosis
Tracheo-oesophageal fistula
Oesophageal atresia and stenosis
Anomalies of upper alimentary tract
Unspecified anomalies of upper alimentary tract
Meckel's diverticulum
Anomalies of intestinal fixation
Hirschsprung's disease
Atresia and stenosis of rectum and anal canal
Anomalies of intestine
Atresia of biliary ducts
Anomalies of gallbladder, bile ducts, and liver
Anomalies of pancreas
Anomalies of digestive system
Unspecified anomaly of digestive system
Indeterminate sex
Undescended testicle
Hypospadias

X - Linked Diseases

Unspecified ovarian dysfunction
Rickets, late effect
Albinism
Disorders involving metabolism of minerals
Congenital disorders of metabolism
Agammaglobulinaemia
Hypogammaglobulinaemia
G-6-PD deficiency anaemia
Hereditary haemolytic anaemia
Hypochromic anaemia with iron loading
Haemophilia A
Haemophilia B

Coagulation defect
Moderate idiopathic mental retardation
Progressive muscular dystrophy
Myotonia atrophica
Colour blindness
Unspecified disease of retina and optic nerve
Congenital hydrocephalus
Pseudohermaphroditism
Generalized anomalies of skeleton
Anomalies of skin
Unspecified anomaly of skin, hair or nails
Syndromes affecting multiple systems

Appendix 3E

Genetic Diseases of Humans (Some Cases) By Class (UNSCEAR 1977 Tables 1,2, 3,and 7 (Annex H) with modifications)

Autosomal Recessive Diseases

Cretinism of congenital origin
Anterior pituitary hypofunction
Unspecified disease of pituitary gland
Phenylketonuria
Albinism
Congenital disorders of amino acid metabolism
Von Gierke's disease
Unspecified glycogen storage disease
Galactosaemia
Lipid storage disorders
Cystic fibrosis
Hepatolenticular degeneration
Disorders involving metabolism of minerals
Disorders of steroid metabolism
Congenital disorders of metabolism
Agammaglobulinaemia
Hypogammaglobulinaemia
Unspecified metabolic diseases
Mediterranean anaemia
Aplastic anaemia
Mild idiopathic mental retardation
Unspecified idiopathic mental retardation
Neuropathic muscular atrophy
Familial progressive spinal muscular atrophy
Amyotonia congenita
Progressive muscular dystrophy
Hereditary spinal ataxia
Amaurotic family idiocy
Progressive cerebral leukodystrophy
Unspecified hereditary diseases of nervous system
Unspecified diseases of retina and optic nerve
Deafness, both ears
Impairment of hearing, one or both ears
Nephritis, unqualified
Congenital hydrocephalus
Microcephalus
Congenital anomalies of nervous system
Micropthalmos
Buphthalmos
Congenital cataract
Anomaly of aorta
Unspecified anomaly of circulatory system
Atresia of billary ducts
Pseudohermaphroditism
Cystic kidney disease
Chondrodystrophy
Generalized anomalies of skeleton
Anomalies of skin
Syndromes affecting multiple systems

Dominant Disorders

Familial acholuric jaundice
Vascular haemophilia
Moderate idiopathic mental retardation
Severe idiopathic mental retardation
Profound idiopathic mental retardation
Neuropathic muscular atrophy
Myotonia atrophica
Unspecified neuromuscular disorder
Hereditary chorea
Facial paralysis
Polyneuritis and polyradiculitis
Horner's syndrome
Unspecified disease of retina and optic nerve
Impairment of hearing, one or both ears
Hereditary disturbances in tooth structure
Myositis ossificans
Neurofibromatosis
Buphthalmos
Congenital cataract
Aniridia
Congenital blepharoptosis
Anomalies of eye
Hypospadias
Cystic kidney disease
Polydactyly
Reduction deformity of upper limb
Reduction deformity of lower limb
Anomaly of upper limb (including shoulder girdle)
Generalized flexion contracture of limb joints
Anomalies of skull and face bones
Chondrodystrophy
Osteogenesis imperfecta
Generalized anomalies of skeleton
Hereditary oedema of legs
Anomalies of skin
Unspecified anomalies of skin, hair and nails
Tuberous sclerosis
Congenital syndrome, affecting multiple systems

Appendix 3F

Years of Life Lost For Genetic Diseases (UNSCEAR 1982 Tables 46-49 (Annex I) with modified titles)

Estimates of Load From Monogenic Dominant Disorders

Condition	Birth frequency per 10^4	Average years of Un-impaired life	Average years of Impaired life and degree of impairment	Lost life years	Cause of death
Familial hypercholesterolaemia	20	55	10 (50 %)	5	Coronary thrombosis
Deafness - congenital (dominant)	1	0	70 (30 %)	0	none
- adult onset	10	30	40 (20 %)	0	none
Polycystic kidney	8	30	10 (50 %)	30	Renal failure
Huntington's chorea	5	45	15 (50 %)	10	Cerebral degeneration and infection
Multiple exostosis	0.5	15	50 (20 %)	5	Cancer
Neurofibromatosis	4	20	30 (50 %)	20	Cancer
Retinoblastoma (untreated) (dominant)	0.3	2	1 (50 %)	67	Cancer
Myotonic dystrophy	2	40	10 (50 %)	20	Dementia and infection
Congenital spherocytosis	2	10	30 (10 %)	30	Haemolytic crisis
Blindness, early onset (dominant)	1	10	60 (50 %)	0	none
Tuberose sclerosis	1	5	45 (80 %)	20	Dementia and infection
Multiple polyposis	1	30	5 (50 %)	35	Cancer
Osteogenesis imperfecta	0.4	2	63 (40 %)	5	Infection
Marfan syndrome	0.4	30	20 (30 %)	20	Aortic aneurysm
Peroneal muscular atrophy (dominant)	2	10	60 (20 %)	0	none
Spastic paraplegia (dominant)	0.5	20	50 (30 %)	0	Infection
Cerebellar ataxia (dominant)	0.5	35	25 (50 %)	10	Infection

Estimates of Load From Autosomal Recessive Disorders

Condition	Birth frequency per 10^4	Average years of Un-impaired life	Average years of Impaired life and degree of impairment	Lost life years	Cause of death
Cystic fibrosis (untreated)	5	2	8 (50 %)	60	Lung infection
Phenylketonuria	1	0	40 (95 %)	30	Infection
Neurogenic muscle atrophy	1	1	4 (90 %)	65	Paralysis and infection
Adrenal hyperplasia	1	0	60 (30 %)	10	Electrolyte loss
Congenital deafness (recessive)	2	0	70 (50 %)	0	none
Early onset blindness (recessive)	1	5	65 (50 %)	0	none
Non-specific mental retardation (recessive)	5	0	50 (90 %)	20	Infection

Estimates of Load From X-linked Recessive Disorders

Condition	Birth frequency per 10^4 males	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Muscular dystrophy (Duchenne type)	2	4	16 (60 %)	50	Debility and intercurrent infection
Haemophilia A	1	0	50 (20 %)	20	Haemorrhage
X-linked ichthyosis	1	0	70 (15 %)	0	none
X-linked forms of mental retardation	1	0	50 (80 %)	20	Intercurrent infection

Estimates of Load From Some Selected Chromosomal Disorders

Condition	Birth frequency per 10^4	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Down's syndrome	12	0	35 (95 %)	35	Associated malformation or infection
Edward's syndrome	1	0	1 (100%)	69	"
Autosomal structural aneuploidy	5	0	20 (95 %)	50	"
XXX	5	5	65 (30 %)	0	none
XXY	5	5	65 (30 %)	0	none
XYY	5	5	65 (20 %)	0	none

Appendix 3G

DEMOGRAPHIC DATA AND COMPUTER PROGRAMS

Three programs were written for this report: DOMINANT, X-LINKED, and TRANSLOCATIONS. Each of the programs is a modification of a program, PROJECT, written originally by Keyfitz and Flieger. They are female-dominant, one-locus models. For low doses, however, they give reasonable approximations if used with genomic induction rates. The programs utilize demograhic data presented in five-year intervals (the only data readily available) and they project population structure by five-year intervals. This means, of course, that the dose projected to result from a nuclear accident must also be accumulated in five-year increments.

All three programs are written in (Microsoft) BASIC for an Apple II computer equipped with a 280 card and an 80 column card. All are of similar structure and may be described as a group (see Figure 3G.1).

INPUT:

(1) Normal demographic data file: Age-specific life tables for normal males and females. Age-specific maternity function for normal females.

(2) Mutant demographic data file: Age-specific life tables for mutant males and females. Age-specific maternity function for mutant females.

(3) Doses (in rem) by five year intervals following a nuclear accident. Assumed to be the same for two sexes.

(4) Coefficients (α and β) of linear quadratic dose response curve for males and females (β may be zero).

(5) Background mutation rates for males and females (usually assumed to be zero, in which case the programs generate the induced cases only).

(6) Last year of projection (projections beyond 150 years are probably meaningless).

(7) In TRANSLOCATIONS there is, in addition, the requirement for two sets of segregation parameters. The segregation ratios in newly arisen translocation carriers: u1, u2, u3, and v1, v2, v3 are for normal, balanced, and unbalanced gametes in females and males, respectively; and the segregation ratios in inherited translocation heterozygotes: XNF, XBF, XUF, and XNM, XBN, XUN are for females and males, respectively.

OUTPUT:

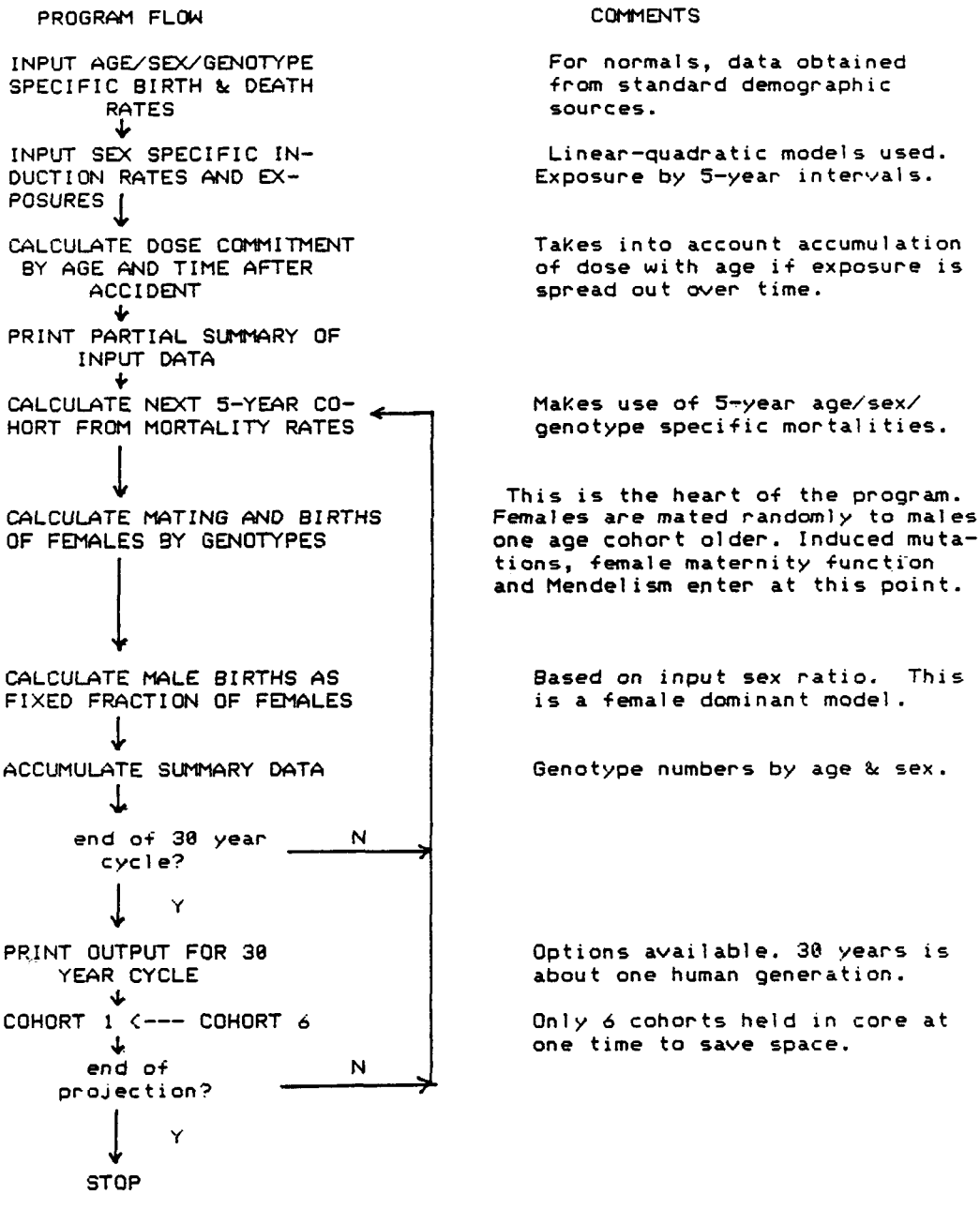
(1) Numbers of individuals by genotype and age projected into the future by five-year intervals and a summary of projections with cumulative totals; or,

(2) Same as above with normals suppressed; or,

(3) Summary only.

An example and interpretation of summary output from the program XLINKED is shown in Table 3G.1.

Figure 3G.1 Structure common to DOMINANT, XLINKED and TRANSLOCATION programs



BNM = normal male births.
BNF = normal female births.
BMM = mutant (heterozygote) male births.
BMF = mutant (heterozygote) female births.
C . . . = cumulative . . .
P . . . = proportion of . . .
CP . . . = cumulative proportion of . . .
TOT = total population size (all ages).
BHF = heterozygous female births (X-linked gene).
BTM = translocation carrier male births.
BTF = translocation carrier female births.
UTM = unbalanced translocation carrier male births.
UTF = unbalanced translocation carrier female births.

The demographic files used were:

USWHT1: This file contains the survival rates of males and females from the 1978 U.S. census data in five-year increments and the maternity function from the same source increased somewhat to make the population approximately stable (the 1978 census showed a negative intrinsic rate of growth).

MUTDOML: Assigns zero survival to heterozygous and homozygous mutants for all ages after five years; used for lethal dominant conditions and aneuploids.

MUTDOMT: Assigns normal survival and fecundity (modified 1978 data) to mutant heterozygotes and zero survival after 5 years to mutant homozygotes. Used to represent condition like Huntington's chorea, a gene against which little selection. This file also used in TRANS program in which normal survival and fecundity assigned to translocation heterozygotes (balanced) and zero survival to unbalanced individuals.

MUTXL: Assigns zero viability to male mutants and female mutant homozygotes, normal suvival and fecundity to heterozygote females. Used for lethal X-linked recessives.

MUTXN: Assigns normal viability to male mutants, normal survival and fecundity to heterozygote females, and zero survival to homozygous mutant females. Used for an X-linked recessive disorder acting in older age groups (little selection against it).

MUTDT8: Assigns 80% viability to mutant heterozygotes and zero viability to mutant homozygotes. Used for 80% viability runs of dominant traits.

MUTXN8: Assigns 80% viability to mutant homozygous males and zero viability to mutant homozygous females. Used for 80% viability runs of X-linked traits.

Table 3G.1 Example output from the program XLINKED.

B:USWHT1 B:MUTXN8
ALPHA AND BETA FOR MALES = .0000072 0
ALPHA AND BETA FOR FEMALES = 0 0
BKGRD MUTATION RATE(MALES) = 0
BKGRD MUTATION RATE(FEMALES) = 0
DOSES ACCUMULATING IN 5-YEAR INTERVALS

DOSE(1) = 1 DOSE(2) = 0 DOSE(3) = 0 DOSE(4) = 0

	1978	1983	1988	1993	1998	2003
BNM	0	44804	45113	42697	39789	39033
BNF	0	42355	42647	40363	37614	36899
BMM	0.000	0.000	0.000	0.000	0.010	0.045
BHF	0.000	0.305	0.307	0.291	0.281	0.308
CBNM	0	44804	89917	132614	172403	211435
CBNF	0	42355	85002	125365	162978	199877
CBMM	0	0	0	0	0	0
CBHF	0	0	1	1	1	1
PBMM		0.000000	0.000000	0.000000	0.000000	0.000001
PBHF		0.000007	0.000007	0.000007	0.000007	0.000008
CPBMM		0.000000	0.000000	0.000000	0.000000	0.000000
CPBHF		0.000007	0.000007	0.000007	0.000007	0.000007
TOT	1000000	1040950	1077360	1106560	1126280	1140780

This is the beginning of a run using the standard demographic file for normals, USWHT1, and the demographic files for mutants, MUTXN8, which assigns a viability of 80% to mutant males. The induction equation used is yield = 7.2E-6 x Dose (the beta term of the linear quadratic is ignored because of the low dose, 1 rad, for this run). The 1 rad is delivered within the first five years following the accident (one weakness of these models is, of course, that 5 years is the smallest time interval within which dose may be delivered).

In 1978 we begin with a total population of one million. There are no induced mutations. By 1983, five years after the accident, there have been 44804 normal male births, 42355 normal female births, 0 hemizygous male induced mutants, and 0.305 (expected) induced female heterozygote births. The cumulative numbers are the same as the interval numbers since this is the first interval. CBHF (cumulative births fo heterozygous females) is 0 because these cumulative totals are rounded to the nearest integer. The proportion of females births who were heterozygotes is 0.000007. The five-year interval before the year 2003 produced 39033 male births, 0.045 hemizygous male births and 0.308 heterozygous female births. By 2003 there had been a total of 211435 normal males but the cumulative mutant total is still below 1/2. The total population size is now 1140780 (somewhat bigger despite the slight negative intrinsic rate of growth because stable age equilibrium has not yet been attained).

In our opinion, the runs using USWHT1 (that is, using the survival rates for 1978 American Whites and their births rates increased slightly to make an approximately stable population size) are probably the more realistic. It is likely that the negative intrinsic rate of growth seen in the 1978 population will not be sustained. In any event, the numbers are easier to interpret with an approximately stable population. The population increases at first in USWHT1 because the US population is not in age structure equilibrium.

Appendix A

THYROID EFFECTS

H. Maxon, S. Thomas, C. Buncher, S. Book, and V. Hertzberg

Executive Summary

Risk coefficients for thyroid disorders have been developed for both ^{131}I and external x or gamma low-LET radiation. A linear, no-threshold model has been used for thyroid neoplasms. A linear, threshold model has been used for other thyroid disorders. Improvements since the Reactor Safety Study (USNRC, 1975) were made possible by relevant new animal and human data. Major changes include the following:

1. Animal data are used to supplement the human experience where necessary.
2. A "specific risk estimate" model is used for thyroid neoplasms, which accounts for observed effects of gender and age at exposure on risk.
3. For thyroid cancer, the basis of the risk coefficients is the experience of North Americans following x-irradiation for benign disease in childhood. This recognizes possible differences in susceptibility in people of different heritage.
4. A minimum induction period for thyroid neoplasms following irradiation is used to define periods at risk.
5. An upper bound risk coefficient for cancer induction following exposure to ^{131}I is based on human experience at relatively low dose exposures.

While the overall lifetime risks of death due to thyroid cancer are consistent with projections by the ICRP (1977), BEIR III (NAS, 1980), and UNSCEAR (1977) Reports, the current model permits greater flexibility in determining risk for population subgroups.

A.1 Introduction

The purpose of this report is to provide a practical assessment of the risk of both benign and malignant thyroidal effects following exposure of the human thyroid gland to external gamma or x-irradiation or internally deposited ^{131}I. In the preparation of this report, extensive use has been made of information contained in a report being prepared by the National Council on Radiation Protection and Measurements entitled "Induction of Thyroid Cancer by Ionizing Radiation".

A specific risk estimate model is used in which a series of absolute risk estimates are modified according to age at exposure, gender, source of radiation, and the dose range under consideration (Table A.3). The specific risk estimate model for thyroidal effects is considered to be a practical alternative to either traditional single absolute risk or relative risk calculations because: 1). estimates of radiation effects necessarily are based almost entirely on persons exposed in childhood, and 2). there are large variations in the so-called "natural" occurrence of thyroid neoplasms or dysfunction in different populations around the world.

In its simplest form, the absolute risk coefficient is estimated by

$$R = \frac{C}{n} \bullet \frac{10^4}{D \bullet y} \qquad \text{(A.1)}$$

Where R = absolute risk coefficient, the number of cases attributable to irradiation per 10^4 subjects per Gy per year at risk; C = the number of excess cases attributable to the radiation exposure; n = the number of subjects at risk in the irradiated population; D = the average radiation dose (in Gy) to the thyroid; and y = the average number of observed years at risk per subject. Detailed discussions of the various components in the equation are presented and appropriate qualifying statements accompany each estimate of the absolute risk coefficient [hereafter referred to as the absolute risk (estimate)].

The assumption of a linear dose-response model over a specific dose range is implicit in the risk estimates used in this report. Because most available data necessarily are derived from higher exposures, extrapolation from such exposures to lower dose levels is necessary. While the linear dose response model is only a first-order approximation, it expresses the average risk per unit of radiation dose over the entire fitted dose range (Land, 1980).

Various factors in human thyroid cancer induction by external x-irradiation have been evaluated by Shore (1980). He examined the dose-response relationship for thyroid cancer 5 to 39 years after exposure in a group of people irradiated in childhood for an enlarged thymus. A "highly significant linear component and a significant quadratic component" were noted, although the author indicated that the precision of the analysis was limited because of the small number of cases of thyroid cancer. The deviation of the linear regression slope from the observed values was not great at low doses. However, the risk in lower dose groups appeared to be overestimated by a factor of about 2 by a strictly linear model derived from the entire population, possibly reflecting effects of the multiple higher dose fractions in the subjects receiving higher total doses. Obviously, potential errors in the linear absolute risk model will vary depending on the dose range being fitted. These data suggest that, for doses in the range of about 0.2 to 10 Gy, a linear model may best approximate risk from 0.5 to 6 Gy, though it may underestimate risk for doses higher than 6 Gy and overestimate risk for doses lower than 0.5 Gy.

Wakabayashi *et al.* (1983) examined the incidence of thyroid cancer in the atomic bomb survivors at Nagasaki in an attempt to clarify the shape of the dose response curve for thyroid cancer. The linear term in a linear-quadratic model was significant whereas the quadratic term was not. A pure quadratic model did not fit well for thyroid cancer. They concluded that the linear model produced the best fit for their data, but mentioned that they could not distinguish statistically one model from the other.

A.2 Thyroid Nodules in the General Population

For estimates of the spontaneous incidence or prevalence of thyroid nodules and of thyroid cancer in the general population, only clinically evident disease is included. There is no attempt to take into consideration the problem of so-called "occult" thyroid cancer which, with rare exception, is only incidentally noted by the pathologist (Sampson, 1976). Because tumor registry data underestimate the actual prevalence of disease, studies containing data relating to the spontaneous prevalence of clinically detectable nodules were examined first.

Maxon *et al.* (1977) combined data on the prevalence of clinically detectable thyroid nodules in an adult English population of 2763 people 18 years of age or older (Tunbridge, 1975) with similar data from the Framingham study of 5127 adult Americans between the ages of 30 and 65 years (Vander, *et al.*, 1968). Palpable nodules were found in 8.9% (386/4326) of the women and in 1.8% (65/3564) of the men in the combined population of the two studies. In addition, Mortensen *et al.* (1955) reported palpable nodules in 44 of 887 persons (5%) whose median age was approximately 60 years.

Rallison *et al.* (1975) examined 2271 children in Arizona who were from 11 to 18 years of age and who had no known exposure (other than natural background) to radiation. Palpable thyroid nodules were found in 33 of them (1.5%). A survey of 7785 children from Michigan, Kentucky, Georgia and Texas who were between the ages of 9 and 16 years found irregular thyroid enlargement and/or definite thyroid nodules in 17 subjects, or approximately 0.22% (Trowbridge *et al.*, 1975).

In calculating the number of expected cancers from the number of total thyroid nodules, 10% of the nodules are assumed to be malignant in patients below age 20, and a rate of 12% is used for patients over age 20 based on previous findings of Messaris *et al.* (1973). For the current calculations, a linear regression function was fitted to these data points, weighting each study equally. The resulting estimate of the spontaneous incidence of clinically detectable thyroid cancer is 0.01% per year of life for the general population.

Data from the Third National Cancer Survey carried out at about the same time indicate that the overall age-adjusted incidence of thyroid cancer for both genders, all ages and races combined, is 3.6 per 100,000 population or 0.0036% per year for those geographic locations represented in both the Second and Third National Survey (Third National Cancer Survey, 1975). The difference between the estimates of thyroid cancer incidence based on clinical examinations (0.01% per year) and the incidence in the National Survey (0.0036% per year) suggests that registry data underestimate the true incidence by a factor of 2-3. Therefore, the projected incidence of 0.01% per year is used when the incidence of thyroid cancer in nonirradiated control groups is not reported.

A.2.1 Minimum Induction Period for Thyroid Cancer

For all studies of radiation-associated solid (nonleukemic) cancers, some period of time exists between radiation exposure and the detection of the first cancer. This span of time has been referred to as the minimum induction period and has generally been considered to be between 5 and 15 years for solid cancers (Land, 1980).

Beach and Dolphin (1962) and Raventos and Winship (1964) examined a total of 660 cases of thyroid cancer occurring in a group of people who had received external radiation in childhood. Based on these data, the times from irradiation to detection of the cancer had a log-normal distribution with a cumulative frequency that showed a rapid increase to a plateau about 15 to 25 years after exposure. When data on the 660 individual patients were combined, the time interval between irradiation and appearance of thyroid cancers had a mean value of 10.5 years with two standard deviation limits of 3.6 to 30.8 years. These data were limited in time of follow-up, which may have resulted in shortening of the estimated mean time from exposure to the development of the cancer (Shore, 1980). On the other hand, the time interval from irradiation to detection of the cancer is longer than the interval between radiation exposure and the initial growth of the neoplasms. In a group of patients with thyroid cancers following external radiation in childhood, Winship and Rosvoll (1970) found, retrospectively, that the average interval between early clinical evidence of a cancer and its confirmation at surgery was almost 2 years. Thus, studies that do not follow patients prospectively from the time of irradiation to the detection of the cancer may overestimate the minimum induction period for thyroid cancer.

Data from the Marshallese followed prospectively after exposure to fallout from nuclear weapons tests (Conard, 1980, 1984) indicate that thyroid cancers first appeared 8 years after exposure. In a study of Japanese survivors of the atomic bombs, Kato and Schull (1982) considered nonthyroidal cancers and indicated that no solid cancers attributable to radiation occurred less than 5 years after exposure. There was also no relationship between radiation dose and induction period in the Japanese atomic bomb survivors.

The earliest thyroid cancer noted in a group of people who received thymic irradiation in childhood in Rochester, New York, occurred 6 years after exposure (Shore, 1980). In Chicago (Roudebush *et al.*, 1978), 6 out of 91 (6.6%) thyroid cancers found in a group of radiation treated patients developed within the first 10 years after exposure. Shore (1984) reviewed this question of a minimum induction period for thyroid cancer following radiation to the thyroid and concluded that 5 years is a reasonable estimate based on human data.

In this report a minimum induction period of 5 years will be used in the calculation of risk and will be subtracted from the mean follow-up time reported in determining person-years at risk.

A.2.2 Average Time at Risk and Duration of Risk

It is difficult to determine the limits of the mean number of observed years at risk (y in equation [A.1]). The difference between the latent period (defined as the amount of time elapsed between radiation exposure and the detection of the thyroid cancer) and the minimum induction period for thyroid cancer of 5 years is assumed to represent the number of years at risk in patients with proven thyroid cancer. If no cancer is detected, the time interval from 5 years after exposure (the minimum induction period) to the follow-up examination is used as the number of years at risk. In cases of multiple exposures over long periods

of time, the mean time between the first and the last exposure is taken as the time at which the total exposure occurred.

The duration of risk of thyroid carcinogenesis following radiation exposure (Y in equation [A.3]) has not been defined because of the limited follow-up time of most studies. Shore (1980) has shown that for people exposed in childhood there appears to be a continuing increase in thyroid cancer cases from 5 to 40 years after irradiation. Goolden (1958) has reported the occurrence of thyroid cancer as long as 40 years after irradiation, although De Groot *et al.* (1983) have reported data that suggest that there may be as much as a 60% decrease in risk after 40 years postirradiation. Similarly, in the most recent survey of the thymic-irradiated children in Rochester, New York (Woodard, 1980) the risk of new thyroid cancer 25 to 33 years postexposure was only about 40% of the risk from 5 to 25 years post exposure. All of these data are based on people receiving x-irradiation for benign disease in childhood at doses below 20 Gy and suggest that, for such exposures, a model that projects a constant risk continuing for more than 40 to 45 years may overestimate the lifetime risk for people exposed in childhood.

Because the median age of the U.S. population in 1980 was about 30 years with about 46 years of average additional life expectancy for that age group, cumulative lifetime risks for the United States population are presented that assume an arbitrary mean life expectancy of 46 years after exposure to the general population. The corresponding mean number of years at risk would be 41. Schematically, the relationship between annual risk and time since exposure might be that shown in Figure A.1. The linear risk coefficient would represent average risk over the entire time frame in question. For population projections it would seem appropriate to use the mean remaining lifetime after exposure minus the minimum induction period as the length of the period at risk for radiation-associated thyroid neoplasms.

A.3 Thyroid Carcinogenesis After Exposure to External Radiation Doses of Less Than 15 Gy

A.3.1 Evidence from North America

The majority of human experience relates to thyroid cancers developing in people treated with external x-irradiation in childhood for benign disease. The largest North American series are those of Hempelmann *et al.* (1975) at the University of Rochester in Rochester, New York; of Maxon *et al.* (1980) at the University of Cincinnati in Cincinnati, Ohio; of Shore *et al.* (1976) in New York City; and of Frohman *et al.* (1977) at the Michael Reese Hospital, and De Groot *et al.* (1983) at the University of Chicago in Chicago, Illinois.

The University of Rochester study compared 2872 young adults who had been given x-ray therapy for presumed thymic enlargement in infancy to 5055 nonirradiated siblings. Thyroid exposures ranged between 0.17 and 6.85 Gy for the various cohorts in the study, with an average exposure of 1.19 Gy. Follow-up was obtained using 4 mail surveys between 1953 and 1971. The mean number of years of follow-up was 24.2 for the irradiated and 22.9 for the nonirradiated subjects. Twenty-four thyroid cancers were found in the irradiated group, compared to none in the controls. The study included one subgroup (Group C) of 261 irradiated persons who had received relatively higher radiation doses, had been followed longer, and had a much higher proportion of Jewish subjects. Altogether, this subgroup of 261 persons contributed 13 of the 24 thyroid cancers found. Hempelmann also noted that 11 of the 24 cases were present in the 8% of the total population at risk which was Jewish. The relative

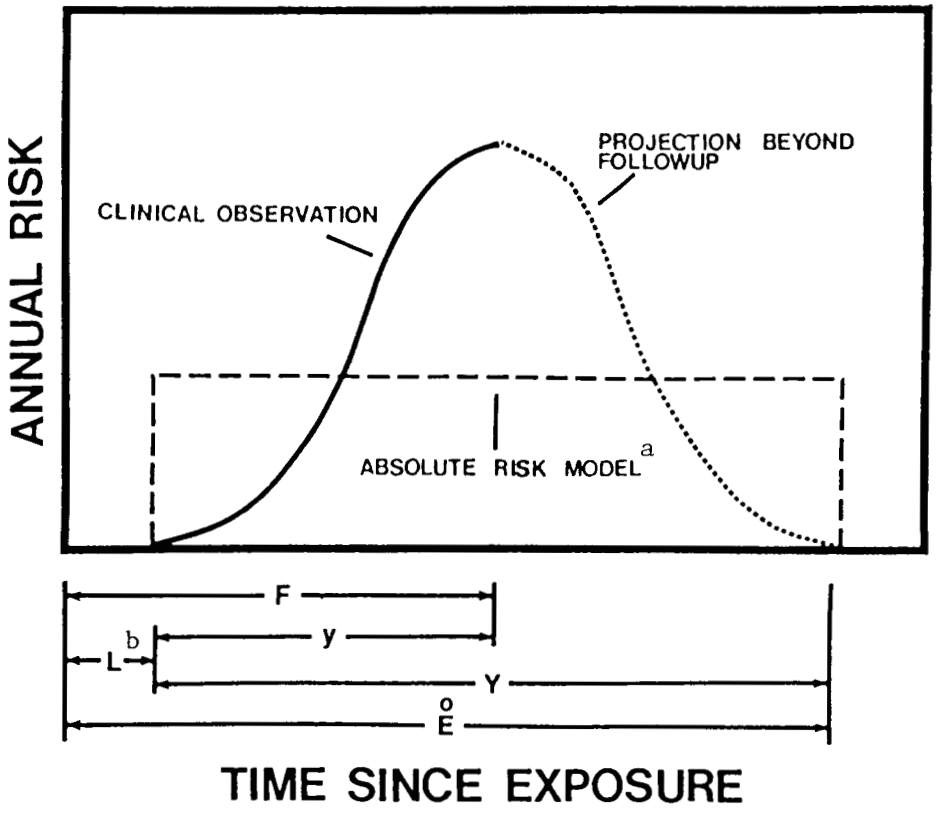


Figure A.1 Annual Risk of Excess Cancer as a Function of Time Since Exposure

Notation Used:

F = Length of clinical followup
L = minimum induction (latency) period
$\overset{o}{E}$ = remaining life expectancy
y = observed interval of risk in clinical followup
Y = interval of risk (expression period)

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[a] The area under the curve showing the expected distribution of cases over time is equal to the area under the absolute risk model.

[b] In the other sections of this report this interval is referred to as the latency period.

risk for Jews compared to nonJews was about 3.5 after adjustment for gender, time since irradiation, and radiation dose (Shore, 1980). Gender seemed to be an additional risk factor since the male-female ratio in the patients with cancer was about 0.4 compared to a ratio of 1.4 for the entire cohort. For the group as a whole, the absolute risk was about 3.8 cases per 10^4 person years at risk (PY) per Gy. If the Jewish subjects were excluded, the absolute risk of thyroid cancer was about 2 cases per 10^4 PY per Gy (Shore, 1980).

In preliminary reports of a subsequent survey from 1979-1980, an additional 5 thyroid cancers were found in the irradiated group over the intervening 8 years compared to 1 new case in the control group (Woodard, 1980). Thus, the approximate absolute risk over this 8 year period beginning about 25 years post irradiation would be about 1.6 cases per 10^4 PY per Gy.

In the University of Cincinnati study, 1266 subjects who received external radiotherapy for a variety of benign diseases in childhood were compared to 958 age-, gender-, race-, and disease-matched people who had received nonradiation therapies. In addition, a comparison of 9865 family members of the two cohorts revealed no evidence of a familial bias toward thyroid disease in the irradiated group. Follow-up was via interviews conducted by specially trained registered nurses, with a mean follow-up time of 21.5 years. The mean thyroid radiation dose to the irradiated cohort was approximately 2.9 Gy. A total of 12 thyroid cancers were found in the 1266 subjects, and 1 was found in the 958 controls, for an excess of about 11 cases in the irradiated group. The mean estimated total radiation dose to the thyroid for subjects with thyroid cancer was 5.24 Gy, with a median value of 3.9 Gy and a range of 2.1 to 11.2 Gy. The male-female ratio in the thyroid cancer patients was 0.6, compared to a value of 1.3 in the overall irradiated cohort. The irradiated men with thyroid cancer had about a 20% higher mean thyroidal dose than irradiated women with thyroid cancer, and their mean latent period (15.7 years) was somewhat shorter than that of the women (22.7 years). The entire study population, drawn from religious-affiliated hospitals other than the Jewish Hospital and from the charity hospitals, was predominantly nonJewish and Caucasian. The absolute risk of thyroid cancer was 1.8 cases per 10^4 PY per Gy.

In New York, Shore *et al.* (1976) evaluated 2215 subjects treated in childhood with irradiation for *Tinea capitis* and compared them to 1395 nonirradiated control subjects who had had *Tinea capitis.* Thyroid doses were estimated to be about 0.04 to 0.08 Gy (mean calculated to be 0.06 Gy) and the average interval of follow-up was about 20 years. No thyroid cancers were found in the irradiated group. The irradiated cohort in this study contained approximately 24% Negro and 11% Jewish subjects.

At the Michael Reese Hospital in Chicago, individuals were identified as having received external radiation to the head, neck, or chest prior to or during adolescence and 2189 of 5226 were contacted and judged to have adequate data for inclusion in the study. A total of 1476 out of the 2189 subjects were actually examined and were considered representative of the entire study group. The mean follow-up time was about 28 years (Frohman *et al.*, 1977). The total population received an average thyroidal dose of 8.08 Gy. About 90% were less than 10 years of age at exposure. No control (nonirradiated) population was evaluated. Surgery was recommended for 402 patients, of whom 327 underwent surgery. Of the total 92 cancers found in the 327 subjects undergoing surgery, 31 (34%) were 5 mm or less in diameter. Such cancers are rarely fatal (Sampson, 1976) and are considered to have little clinical effect (Sampson *et al.*, 1969). If lesions less than 5 mm in diameter that were only incidentally

noted at surgery for other reasons are excluded, then one can predict that about 75 cancers greater than 5 mm in diameter would be found in the group of 402 irradiated subjects for whom surgery was recommended. Based on the calculations of the prevalence of clinically evident thyroid cancer in the general population aged 20 to 29 years, 3-4 clinically detectable thyroid cancers would be expected for a radiation associated excess of about 70 cases. The resultant absolute risk in this group of 1476 examined people is about 2.6 cases per 10^4 PY per Gy. Although not originally mentioned by the investigators, the population in the Michael Reese study had a high proportion (75-90%) of Jewish patients and less than 1% nonCaucasian patients (Frohman, 1983). No correlation was observed between age at exposure or gender and the subsequent development of thyroid cancer.

A University of Chicago study (De Groot *et al.*, 1983) evaluated 416 subjects who were referred with a history of prior head or neck irradiation for benign, nonthyroidal disease in childhood. About 63% (263/416) of the patients had also been considered by the referring individual to have possible thyroid abnormalities and thus are highly selected. The total number of irradiated people from whom these patients were selected is unknown precluding the use of these data for the calculation of numerical risk estimates. The mean age at irradiation was 7.1 years with a mean thyroidal dose of 4.51 Gy. The average time between exposure and examination was 26.4 years. Thyroid cancers were found at surgery in 41 people, and 35 of the cancers were greater than 5 mm in diameter. Nonirradiated control subjects were not evaluated. But on the basis of a spontaneous incidence of 0.01% per year of life, 1.4 cases would be predicted.

During a prospective follow-up of a subgroup of 130 patients for more than 5 years after an initial examination that did not indicate cancer, the incidence of new cancer cases was less with an apparent risk about 30% of that calculated for the group as a whole. This observation may reflect the prior patient selection and/or a true decline in the incidence of thyroid cancer as time increases following irradiation. Among 391 patients examined up to 40 years after exposure, 40 cancers were found (10.2%); among 25 patients examined 40 years or more after exposure, only 1 cancer (4%) was found. The average time interval between irradiation and examination for patients with thyroid cancer was 23.8 ± 7.0 years (range 10 to 40 years), and less than 1% of the patients were examined within the first 10 years after exposure. The incidence of thyroid cancer in men was about 1.6 times that in women, reflecting the very selected subgroup of patients being examined.

When the results of several studies from the United States are combined (Table A.1), an excess of 109 thyroid cancers is found in 7829 subjects, representing about 43×10^4 PY • Gy at risk. The range of mean years follow-up in each study was 20 to 35 years, and the range of mean thyroidal dose in each series was 0.06 to 8.08 Gy. Their composite absolute risk is about 2.5 thyroid cancers per 10^4 PY per Gy with a risk range (based on the risks calculated for each individual study) of 0 to 3.0 thyroid cancers per 10^4 PY per Gy in children exposed to external radiation to the thyroid. The approximate ethnic and gender composition of the irradiated subjects in these studies is shown in Table A.2. While the relatively high proportion of males might tend to lower the risk estimate, this would be offset by the increased risk of Jewish subjects as found in the Rochester, New York, study.

Table A.1 Thyroid Cancer Following Head and Neck X-irradiation for Benign Disease in Childhood in the United States

Source	Number Irradiated	Excess Thyroid Cancers[a]	Mean Years at Risk[b]	Mean Thyroidal Dose (Gy)	Total PY·Gy At Risk
Shore et al. (1976)	2,215	0	15	0.06	1,994
Hempelmann et al. (1975) and Woodard (1980)	2,872	28	27	1.19	92,277
Maxon et al. (1980)	1,266	11	16.5	2.90	60,578
Frohman et al. (1977)	1,476	70	23	8.08	274,300
Pooled Data[c]	7,829	109	21.2	2.45	429,149

[a] Clinically evident disease

[b] Assuming a minimum induction period of 5 years

[c] Obtained by combining data from all four studies, using a weighted average for years at risk and thyroidal dose.

Table A.2 Approximate Ethnic Composition of Irradiated Children

Source	Number Irradiated	Composition of Study Population			
		Caucasian Jewish (%)	Caucasian Non-Jewish (%)	Negro (%)	Male (%)
Shore et al. (1976)	2,215	11	65	24	87
Hempelmann et al. (1975)	2,872	8	91	1	58
Maxon et al. (1980)	1,266	2	90	8	57
Frohman et al. (1983)	1,476	80	20	< 1	60
Pooled Data	7,829	22	69	9	66

A.3.2 Evidence from Israel

Ron and Modan (1984) examined Tumor Registry data for 10,842 subjects who had received x-irradiation to the head for *Tinea capitis* in Israel at a mean age of 7.1 years. The mean follow-up time was 22.8 years, and comparison was made to the same number of nonirradiated, nonsiblings and to 5400 siblings without known radiation exposure (other than natural background). Thyroid cancers were found in 29 of the irradiated group, compared to 8 in the larger, combined control group, for an excess of 24 cases in the irradiated population. Subjects in this study had an estimated mean thyroidal dose of 0.09 Gy with a range of 0.04 to 0.17 Gy. The absolute risk of thyroid cancer in this population was about 14 cases per 10^4 PY per Gy; 23 of the 29 total thyroid cancers in the irradiated group occurred in women, as did 6 of 8 cancers in the nonirradiated controls. The ethnic background was Jewish. The 5420 subjects who were of Moroccan or Tunisian descent were found to have about a 2-fold increase in absolute risk of thyroid cancer compared to the 5422 subjects from Israel, Asia, and other North African areas.

A.3.3 Evidence from the Japanese A-Bomb Survivors

Since 1945, Japanese survivors of the atomic bombs detonated in Hiroshima and Nagasaki have been followed for long term health consequences of their radiation exposures. There are some recent questions about the radiation dosimetry. Most of the controversy has been centered around neutron dosimetry, primarily involving the people in Hiroshima. In the case of Nagasaki, over 90% of the exposed population had calculated neutron doses to the thyroid of less than 0.005 Gy, and neutrons were considered to be responsible for less than 5% of their total thyroidal dose. In addition, the tumor registry data are quite complete in Nagasaki for the 20 year period from 1958 to 1979, representing an interval of 13 to 33 years following exposure. Several recent reports on thyroid cancer in the people of Nagasaki provide useful information regarding gender, age, and dose-response characteristics of thyroid carcinogenesis following high dose rate gamma irradiation to the human thyroid.

Prentice and associates (Prentice *et al.*, 1982) reported clinically evident thyroid cancer (about 60% of total cancers in this registry data) during the period from 1959 to 1979 in 23,884 people who were residents of Nagasaki in 1945, who were still alive in 1959, and who had no documented evidence of thyroid cancer prior to 1959. Radiation doses to the thyroid were based on the so-called T65 dose estimates and were fairly evenly distributed throughout population subgroups derived according to age at exposure and gender. When excess thyroid cancers were calculated according to age group at exposure and gender, there were apparent differences in the incidence of excess cancers. These data suggest that women are more susceptible than men and that younger people are more susceptible than older people. The differences in susceptibility do not appear to be due to differences in radiation dose.

Using the T65 revised dose estimates, Wakabayashi (Wakabayashi *et al.*, 1983) also evaluated the risk of thyroid cancer among the population from Nagasaki. They concluded that the linear model produced the best fit of their data. Their resultant calculated absolute risk of thyroid cancer in the entire exposed population of Nagasaki was 1.3 cases per 10^4 PY per Gy compared to a value of 0.65 cases per 10^4 PY per Gy for men and of 1.9 cases per 10^4 PY per Gy for women.

A.3.4 Lethality of Radiation-Associated Thyroid Cancers

Mortality experience from radiation-associated carcinomas is quite limited. The 1977 UNSCEAR Report (UNSCEAR, 1977) identified 4 deaths in 142 (about 3%) radiation-associated cases of thyroid cancer within a mean of 24 years after exposure. In the thymic-irradiated patients from Rochester, New York, with thyroid cancer (Woodard, 1980), 2 of 28 excess cancers (about 7%) had been fatal over a mean period of 35 years since irradiation.

Roudebush and associates in Chicago (Roudebush *et al.*, 1978) also compared the clinical courses of 91 patients with radiation-associated thyroid cancer to those of 72 control patients with similar carcinomas, but with no history of therapeutic irradiation in childhood. In spite of more aggressive therapy, patients with radiation-associated thyroid cancers had a higher incidence of multicentric disease, local invasion, distant metastases, and recurrences than those without a prior history of x-irradiation. The mean follow-up times after surgery were relatively short, being 10.2 years in the irradiated group and 12.2 years in the control group. Over this time span there were no significant differences in mortality due to thyroid cancer in the two groups. These findings suggest that radiation-associated thyroid cancers are at least as aggressive in their behavior as spontaneously occurring thyroid cancers and are likely, as more experience accumulates, to have a similar mortality to spontaneous thyroid cancers.

Compilations of clinical experience with external radiation-induced thyroid cancers suggest that, with rare exceptions, the tumors are of the well-differentiated adenocarcinoma variety. About 90% of these radiation-associated human carcinomas have been of the papillary type and about 10% have been of the follicular type, using World Health Organization criteria (Roudebush *et al.*, 1978).

In an update of the Mayo Clinic experience with slightly more than 1100 patients, McConahey (1981) found that after 25 years, 5.7% of patients with papillary carcinoma of the thyroid had died of the disease and approximately 18% of those with follicular carcinoma had died of this disease. These observations combined with the prevalence of papillary and follicular carcinomas in irradiated patients suggest that up to about 7% of patients with radiation-induced thyroid cancer may eventually die of their disease over the first 25 years after diagnosis. More deaths would be expected after that time, albeit at a lesser rate (Appendix A.B).

Projections for 1983 from the American Cancer Society (Silverberg and Lubera, 1983) suggest that the mortality rate for all thyroid cancer will be about 12.1% for males and about 9.6% for females, for an average of about 10% in a population composed equally of both genders. Although the mixtures of histologic types may be different in irradiated and nonirradiated people with thyroid cancer, a total thyroid cancer mortality rate of 10% for the United States would seem to be applicable to radiation-associated thyroid cancers. Careful follow-up after irradiation and early medical intervention might lower the mortality rate, although this has not been proven.

A.3.5 Modifying Factors in Radiation-Associated Thyroid Neoplasia

A.3.5.1 Age: Human Studies

The external radiotherapy studies noted previously were overwhelmingly concerned with people irradiated in childhood or adolescence. No equivalently large studies exist on cancer induction from similar therapeutic radiation exposures in adults. There are, however, several populations of heterogeneous age that have been exposed to other types of thyroidal

irradiation; data from these groups can give some insight into the question of the influence of age on thyroid neoplasia.

Dobyns *et al.* (1974) reviewed the results of a 20-year follow-up study on 19,000 patients who received ^{131}I therapy in the treatment of Graves' disease. Of these patients, a significant increase in the number of thyroid adenomas was observed in the youngest quartile of the population (precise ages not stated). Radiation dose comparisons by age group are not available.

Prentice *et al.* (1982) showed a higher incidence of thyroid cancers in people exposed to radiation from the atomic bomb in Nagasaki at age less than age 30 years than in those greater than age 30 at exposure. Parker *et al.* (1971, 1974) suggested that people exposed to radiation from the bombs when under the age of 20 years were at about twice the risk for thyroid cancer of those exposed later in life.

Following nuclear weapons testing in 1954, about 251 native persons living in the Marshall Islands were accidentally exposed to atomic fallout. Thyroid radiation resulted from external gamma irradiation, internally deposited short-lived isotopes of iodine (^{132}I, ^{133}I, ^{134}I, ^{135}I), ^{131}I, and radiotellurium (^{132}Te, ^{131m}Te). The people involved have been carefully observed for adverse health effects, including thyroid cancer. A 26-year follow-up report has been published (Conard *et al.*, 1980) and thyroid dose estimates have been re-evaluated (Lessard *et al.*, 1983). If noncancerous thyroid nodules and hypothyroidism are combined, the prevalence of excess nonmalignant thyroid abnormalities was 25% in subjects less than 10 years of age at exposure, compared to 6.8% in those between 10 and 18 years of age, and 7.1% in those over the age of 18 years. These results may reflect, in part, the higher estimated radiation exposures (up to 52 Gy) to the thyroids in the youngest group, compared to those of the older groups (up to 13 Gy) (Lessard *et al.*, 1983). The higher radiation doses to the younger subjects probably reflected their smaller thyroid gland sizes as well as differences in inhalation and ingestion pathways in the various groups. When thyroid cancer induction alone was examined, no definite age differences were found although the expression of radiation carcinogenesis may have been altered by the administration of thyroid hormone to some of the exposed subjects as well as by intervening surgery for the removal of benign nodules. A total of 7 thyroid cancers was reported initially (Conard *et al.*, 1980), but one of these has been recategorized as benign (Lessard *et al.*, 1983). The prevalence of excess thyroid cancers in the group under the age of 10 years (including *in utero*) at exposure was about 2.2%, compared to about 3.3% in the 10- to 18-year old group; and to about 2.3% in the subjects over the age of 18 years (Lessard *et al.*, 1983).

These limited data from epidemiological studies indicate that age at exposure is a modifying factor for thyroid carcinogenesis because of increased radiosensitivity of the thyroids of children. They suggest about a 2-fold increase in susceptibility to radiation-carcinogenesis for thyroid glands in children and adolescents (18 years of age or less), compared to adults. Possible influences of promoting or modifying factors other than radiosensitivity, which might also contribute to this apparent age-related susceptibility, are not defined.

A.3.5.2 Gender

The studies on subjects exposed to external radiotherapy in childhood suggest that females show a greater effect of radiation carcinogenesis of the thyroid than males exposed

under similar conditions. In the University of Rochester studies (Hempelmann *et al.*, 1975), females had 2.3 times the incidence of males, while in the University of Cincinnati studies (Maxon *et al.*, 1980), the ratio was 2.2. In the Israeli population irradiated for *Tinea capitis* (Ron and Modan, 1984), the excess risk of thyroid cancer in women was about 4 times that for men. In the Marshall Islands subjects (Conard *et al.*, 1980) all 7 cancers occurred in women, and in the Japanese (Parker *et al.*, 1958, 1974) the incidence of excess thyroid cancers in females exceeded that in males in every exposure group. Shore (1980) has demonstrated that whereas the absolute risk of thyroid cancer following thymic irradiation in childhood is significantly higher in women than in men (about 2.8 times as great in women), relative risk calculations do not indicate an increase in risk for women. Similar findings have been reported in Japanese A-bomb survivors where the absolute risk in women is 2.9 times that in men (Wakabayashi *et al.*, 1983). Based on estimates from the Surveillance, Epidemiology, and End Results (SEER) Program of the Biometry Branch of the National Cancer Institute (Silverberg and Lubera, 1983) the female/male risk ratio for thyroid cancer in the general population of the U.S. is 2.5.

These data are consistent with an increased absolute risk of thyroid cancer in females for both spontaneous and radiation-induced thyroid cancer that is at least twice that for males exposed under similar conditions.

A.3.5.3 Ethnic Background

There are some questions regarding the relationship of radiation-induced thyroid cancer to the presence or absence of Jewish heritage. The University of Rochester study (Hempelmann *et al.*, 1975) of 2872 people irradiated in childhood clearly shows that a disproportionate number of cancers (11 of 24 or 46%) were found in the 8% of the population that is Jewish. This same Jewish population contributed 23% of the total PY-Gy in the study. Nevertheless, the relative risk for Jews compared to nonJews was about 3.5 after adjusting for gender, time since irradiation, and radiation dose (Shore, 1980). When the Jewish subjects are excluded, the absolute risk of thyroid cancer becomes about 2 cases per 10^4 PY per Gy, which is close to the value of 1.8 cases per 10^4 PY per Gy found in the predominantly nonJewish Cincinnati study (Maxon *et al.*, 1980). Higher risk estimates were obtained in the Israeli *Tinea capitis* study (Ron and Modan, 1984) ($\tilde{}$ 14 cases per 10^4 PY per Gy) and the Michael Reese Hospital study (Frohman *et al.*, 1977) ($\tilde{}$ 2.6 cases per 10^4 PY per Gy) both of which are predominantly Jewish populations. The reasons for these differences may be related to ethnic background, particularly in light of the absence of cases in similarly (to the Israeli study) irradiated population in the New York *Tinea capitis* study which was 89% nonJewish and 24% Negro (Shore *et al.*, 1976).

It must also be noted that in the Israeli study, the absolute risk of thyroid cancers in the subjects emigrating from Morocco or Tunisia was about twice that for subjects emigrating from other areas (Ron and Modan, 1984), although the differences were not statistically significant due in part to the small number of spontaneous cases in nonirradiated cohorts.

While not clearly related to radiation, it also has been observed that the prevalence of incidentally-noted thyroid cancer at autopsies performed on the general population may be about 3 to 6 times higher in Japanese than in Americans (Fukunaga and Lockett, 1971; Sampson *et al.*, 1969). Within the United States, the prevalence of thyroid cancer varies by ethnic group, with Negro Americans having only about 2/3 the prevalence of Caucasian

Americans and Oriental or Polynesian Americans living in Hawaii having about twice the prevalence of Caucasian Americans living in Hawaii (Silverberg and Lubera, 1983).

These observations indicate that ethnic or genetic backgrounds may be important moderating factors in thyroid carcinogenesis and suggest that risk factors should be modified to reflect the ethnic background of a given population if they are to be applied to that specific population and vice versa.

A.4 Thyroidal Carcinogenesis After Exposure to ^{131}I

A.4.1 Therapeutic ^{131}I for Thyrotoxicosis

A.4.1.1 Adults

Dobyns *et al.* (1974) found that 86 of 16,042 patients with Graves' disease without palpable nodules at the time of radioiodine therapy were subsequently operated and found to have nodules after ^{131}I therapy. The mean follow-up time was only 8 years. Two of these 86 patients were operated on because of recurrent thyrotoxicosis, but in both of these a palpable mass was specifically described in the thyroid. In the other 84, surgery was presumably indicated because of some palpable abnormality (Tompkins, 1976). Nine (9) of the 86 (10.5%) had cancer and 77 (89.5%) had benign lesions. In an additional 494 of 16,042 patients, palpable nodules were found to have developed after ^{131}I therapy, but the 494 had not undergone surgery and have not been systematically followed since the end of the study. Based on the 9 documented cases of thyroid cancer, the prevalence of thyroid cancer in Graves' disease treated with ^{131}I would be about 0.06%, compared to a spontaneous prevalence in Graves' disease of about 0.1%. On the assumption that the prevalence of cancer would be the same in 494 unoperated patients as in the 86 patients subjected to surgery, 52 additional cases of cancer could be postulated. These assumptions would suggest a maximum prevalence of thyroid cancer of about 0.4% following ^{131}I therapy. The radiation dose in each of these patients was calculated to be more than 20 Gy, with a mean of approximately 87.6 Gy to the thyroid, based on an assumption of a 6-day effective half-life (Maxon *et al.*, 1977; O'Connor *et al.*, 1979).

Holm and associates reported on 4557 people with hyperthyroidism who were treated with ^{131}I in Sweden (Holm *et al.* 1980b; Holm, 1984). Their mean follow-up period was 9.5 years and the mean age of subjects was 56 years at exposure. Their mean administered activity of ^{131}I was 13 mCi, calculated to deliver between 60 and 100 Gy in most cases. The subjects were about equally divided between those who had toxic diffuse glands and those who had toxic nodular goiters. A total of 4 thyroid cancers were found, and all were in women with previous toxic nodular goiters treated with a mean total activity of 27.5 mCi ^{131}I. Based on Swedish tumor registry data from nonirradiated women with nodular goiters, 2 cases were predicted. The difference between 2 expected and 4 observed cancers was not significant. In a separate population, Sokal (1954) estimated the prevalence of thyroid cancer in toxic nodular goiter to be 0.94%. Application of this figure to the approximately 1900 women with toxic nodular goiter in the Holm study (1984) results in a prediction of about 18 spontaneous cancers.

In the two populations (Dobyns, *et al.*, 1974; Holm, 1984) a total of 20,599 adult subjects were followed for means of 8 to 10 years. There is no evidence of ^{131}I-induced thyroid carcinogenesis at high dose levels (greater than 20 Gy) in adults. This apparent absence of carcinogenesis may be due in large part to the effects of cell-killing and/or sterilization at such high dose levels and/or to short follow-up times in relatively (compared to children) radioresistant adults.

A.4.1.2 Children

Safa *et al.* (1975) have reported on 273 patients treated between the ages of 1 and 20 years with ^{131}I for Graves' disease. There were 31 additional children aged 16 years or less who were treated with ^{131}I in the Cooperative Thyrotoxicosis Follow-up Study (Tompkins, 1976). Pooling of these observations reveals 2 cases of thyroid cancer in the combined population followed after ^{131}I therapy. Estimates of thyroid dose and follow-up period, available for 271 of 304 subjects, suggest a mean radiation dose of about 90 Gy with a mean follow-up time of about 11 years. The 2 observed cancer cases are more than might be expected spontaneously in Graves' disease (0.3 case), although the difference between the observed and expected is not significant.

A.4.2 Nontherapeutic Exposures to ^{131}I

Holm *et al.* (1980a, 1981) reported a retrospective analysis of outcome in 10,133 subjects exposed to diagnostic administrations of ^{131}I (total less than 1 mCi) for suspected thyroid disease. The population included 8047 females (79%) and 2086 males (21%) with a mean age of 44 years for both genders. Of the 10,133 subjects, 9639 were over the age of 20 years at exposure and 494 were less than 20 years of age. For the 9639 adults, the mean calculated thyroidal dose was 0.58 Gy, whereas, in the 494 younger subjects, the mean dose was 1.59 Gy. Patients were followed for a mean time of 17 years after exposure to ^{131}I. No patients were included who had received external radiation therapy above the diaphragm or who had been treated previously with other internally administered radionuclides. Any cancers diagnosed less than 5 years after the ^{131}I exposure were excluded as not being related to the exposure. The study had insufficient data to take into account possible effects of intervening thyroid hormonal or surgical therapy after the radioiodine exposure on the subsequent development of thyroid cancer. In 8 patients, a thyroid cancer was confirmed as being present. All 8 of the cancers were in the adults; none was found in the children. Six of the 8 cancers (75%) occurred in women and 2 (25%) in men, reflecting the gender ratio of the study population as a whole. This did not represent any significant increase in cancer in the irradiated population. The expected number of thyroid malignancies, computed from age- and gender-specific cancer incidences in the Swedish Cancer Registry, was 8.3 cases.

Since 1973, a national collaborative study of children exposed to diagnostic levels of ^{131}I between 1946 and 1967 has been in progress under the auspices of the Center for Devices and Radiological Health[1] of the U.S. Department of Health and Human Services, with support from the National Cancer Institute and the U.S. Nuclear Regulatory Commission. The study was designed to include about 13,000 potential subjects, equally divided amoung controls,

[1]Formerly the Bureau of Radiological Health.

exposed persons, and siblings of irradiated people (Harris, 1980). No data have been made available since preliminary communications on the initial 443 cases in 1975 (Hamilton and Tomkins, 1975). Those communications suggested that at mean doses of 0.94 Gy to the thyroid, with a range of less than 0.1 to 19 Gy, 6 subjects of 443 who received diagnostic ^{131}I studies in childhood were found to have benign thyroid nodules, and 16 years later none of the 443 was found to have thyroid cancer. There was no significant correlation between estimated thyroidal radiation dose and the incidence of benign nodules.

In a survey of 5179 children, of whom 1378 had been exposed to ^{131}I in radioactive fallout in the western United States, Rallison *et al.* (1974) could find no significant differences between irradiated and nonirradiated subjects in the prevalence of thyroid nodules, benign and malignant, at an average follow-up time of 14 years. The dosimetry is undergoing extensive review, but the revised dose estimates are not yet available. The lowest figure proposed has been a mean thyroidal dose of 0.18 Gy (Rallison *et al.*, 1974) with some other estimates being an order of magnitude higher (BEIR, 1980). Because of the uncertain dosimetry these data have not been used for risk estimates in this report.

For children exposed to diagnostic ^{131}I, the combined studies represent a total of 937 subjects representing 1.4×10^4 PY • Gy at risk. In the case of adults, the Swedish study contains 9639 subjects representing about 6.7×10^4 PY • Gy at risk. If the absolute risk estimates derived earlier from carcinogenesis following external radiation exposures in childhood in the United States were applicable to these populations exposed to ^{131}I, then an excess of about 3-4 thyroid cancers in children and of about 8-9 thyroid cancers in adults would be expected, assuming that adults are at about 1/2 the risk of children. These experiences, with mean thyroidal doses from ^{131}I that are well below 2 Gy, contain no positive evidence of the induction of human thyroid cancer by radiation.

Hanley (Hanley and Lippman-Hand, 1983) has discussed the problem of interpreting zero numerators. To find the largest number of excess cases (which is distributed as a binomial random variable and with which a finding of $0/n$ is still compatible, that is, the data at the upper bound of the 95% confidence level), one may solve the equation:

$$\text{Largest Number of Excess Cases} = 1 - (0.05)^{1/n}$$

In the case of 937 children exposed to relatively low doses from diagnostic ^{131}I, this calculation results in a value of 0.00319 or about 3.2 excess cases/1000 as the upper 95% limit of risk compatible with zero observed cases. If the observed absolute risk of 2.5 excess cases per 10^4 PY per Gy following external irradiation in childhood were applicable, then with 1.4×10^4 PY • Gy at risk one would expect 3.5 cases/937 or about 3.7 cases/1000. For the 9639 adults exposed to diagnostic ^{131}I, similar calculations using an absolute risk following external irradiation of 1.25 excess cases per 10^4 PY per Gy (i.e., adults = 1/2 the risk of children) lead one to expect 0.87 excess cases/1000. The largest number of excess cases compatible with the upper 95% limit of a zero numerator in the adults is 0.31 cases/1000. Since the risk estimate desired for external radiation predicts a larger number of excess cases than the upper 95% limit for what was observed in the ^{131}I exposed patients, then the risk of human thyroidal carcinogenesis following exposure to ^{131}I would appear to be less than the risk following exposure

to the same dose from external x-irradiation.

Another approach to the question of the relative carcinogenicity of ^{131}I and external radiation is the following:

Choi (1978) and Feinstein (1977) have discussed a mathematical model for predicting the minimum number of subjects required in a study of adverse effects characterized by an increased incidence of a spontaneously occurring abnormality. This calculation is based on the normal approximation to the binomial distribution. The number of cases is given by the formula:

$$n = \frac{(Z_\alpha)^2 \bullet P_0 \bullet (1 - P_0)}{(P - P_0)^2}$$

Where Z_α is the standard normal (Gaussian) variate at a specified level of significance α, which is 1.645 for a single tailed test at $\alpha = 0.05$. Implicit in this formula is the assumption of a power of 50% (or $\beta = 0.5$ and $Z_\beta = 0$) in order to approximate a central estimate analogous to the risk calculation for external irradiation. P_0 is the proportion of cases in which thyroid cancer occurs naturally, and P is the proportion of cases in which thyroid cancer occurs after irradiation, including naturally occurring cases. Then $P-P_0$ can be defined by the risk estimate (in cases per 10^4 PY per Gy, see Equation A.1, p. A-4) multiplied by the number of PY • Gy at risk and by 10^{-4}, divided by the number of persons in the population. One may then modify the basic equation to give the risk level at which one would expect to find an excess number of radiation-associated thyroid cancers in a given exposed population at $\alpha = 0.05$ as follows:

$$\text{Risk} = \frac{n \bullet 10^4}{\text{PY} \bullet \text{Gy at risk}} \left[\frac{(1.645)^2 (P_0)(1-P_0)}{n}\right]^{0.5}$$

In applying this formula to the human data following low dose ^{131}I exposures, it would appear that if external radiation and ^{131}I are equally harmful in terms of thyroid cancer induction on a Gy-for-Gy basis, then for the population of 9639 people exposed in adult life in Sweden and representing 6.7 x 10^4 PY • Gy at risk with a spontaneous thyroid cancer rate in the unexposed Swedish population of 8.19 • 10^{-4}, and for a population of 937 people exposed in childhood and representing 1.4 $\times$ 10^4 PY • Gy with a spontaneous rate of thyroid cancer of about 3 • 10^{-4}, then at $\alpha = 0.05$, we should have found an excess of radiation-associated thyroid cancers at risk levels of greater than 0.69 cases per 10^4 PY per Gy in adults and 0.62 cases per 10^4 PY per Gy in children. The calculation in the case of children is less certain due to the small numbers and lack of precise information regarding the actual spontaneous rate of thyroid cancer in the ^{131}I exposed children. In other words, if the risk following ^{131}I exposure is equal to or greater than 0.6 to 0.7 cases per 10^4 PY per Gy, then one should be able to detect the excess cancers at $\alpha = 0.05$. In fact, no excess cancers were determined to be present.

Thus, if one compares the human ^{131}I experience to the human external radiation experience, then the risks of radiation carcinogenesis are not the same from the two sources. It

appears that in people ^{131}I is less carcinogenic on a Gy-for-Gy basis than external radiation, probably no more than about 1/4 to 1/2, if ^{131}I is carcinogenic at all. Precisely how much less has yet to be determined as more human studies on low dose ^{131}I exposures in childhood await satisfactory completion.

A.4.3 Animal Studies

Studies of thyroid cancers in animals exposed to radiation also provide evidence on the relative effectiveness of ^{131}I and external x- or gamma-radiation. As demonstrated in several studies, data at high exposures in Long Evans rats (Lindsay *et al.*, 1957, 1961; Doniach, 1963) and CBA mice (Walinder *et al.*, 1972) support a relative effectiveness factor of up to 1/10 for the production of thyroid cancers, as do data from goitrogen-stimulated hooded Lister rats (Doniach, 1957). Adenoma production in the latter strain also supports a relative effectiveness factor of about 1/10.

At lower doses and dose rates (~ 1-10 Gy), the effects in Long Evans rats (Lee *et al.*, 1982) showed that ^{131}I and x-irradiation each produced thyroid neoplasia. ^{131}I had about the same effectiveness as x-rays for the production of carcinomas at all exposures although a relative effectiveness factor of as low as 1/3 could not be excluded. For adenomas, ^{131}I was about 40% as effective as x-rays at about 10 Gy, but of about the same effectiveness at lower doses.

These limited animal data support a lower relative effectiveness factor for ^{131}I for thyroid carcinogenesis compared to external radiation.

A.5 Conclusion and Recommendations: Carcinogenic Risk to the Human Thyroid Following Exposure to Ionizing Irradiation in Doses of Less Than 15 Gy

Considerations of human experience indicate that ^{131}I is less carcinogenic to the thyroid, per Gy of exposure, than external radiation, if it is carcinogenic at all. This difference in effectiveness is probably due to factors related to dose rate and to dose distribution. Until further data become available, it is recommended that ^{131}I be considered to be 1/3 as effective as external radiation (x-rays) in the induction of thyroid cancer in people. Since the best information regarding thyroidal radiation carcinogenesis in people is from data based on children exposed to external radiation, it is also recommended that those data be used as the basis for the risk calculations.

Women appear to be at twice the risk of men for clinically apparent cancers at a given exposure level. Data suggesting that children are more susceptible than adults warrant a 50% reduction in risk estimates, when estimates derived for people less than or equal to 18 years of age at exposure are applied to a population of adults. The general formula used to calculate age, gender, and radiation source specific risks is shown in Table A.3.

While risk estimates derived from pooled data are useful when considering the effects of exposure, definite ethnic or genetic factors appear to be present which would dictate that risk factors from controlled studies of populations similar to the one at risk should be used whenever possible. For the calculation of risks of fatal cancer, it is assumed that, given reasonable medical diagnosis and care, approximately 10% of the radiation-induced thyroid cancers may be lethal.

Table A.3 Calculation of Age, Sex, and Radiation Source Specific Risk Estimates for Thyroidal Neoplasms

$$SRE = R \cdot F \cdot S \cdot A \cdot Y \cdot L$$

Where:

SRE = Specific risk estimate for risk of thyroid cancer attributable to radiation exposure.

R = Absolute risk estimate (excess cases per 10^4 PY per Gy) for consigned (both sexes), ethnically similar, populations of children exposed to external x-irradiation and correcting for a minimum induction period for thyroid cancer of 5 years.

F = Dose effectiveness reduction factor (1 for external radiation and short-lived iodine isotopes; 1/3 for cancer and 1/5 for benign nodules following ^{131}I.

S = Sex factor (4/3 for women and 2/3 for men, assuming that women are twice as susceptible as men and that the R was derived from a population comprised of equal numbers of both sexes).

A = Age factor (1 for populations age 18 or less at exposure and 1/2 for populations over age 18 at exposure).

Y = Anticipated average number of years at risk for the population in question.

L = Lethality factor of 1/10 for cancer only. The factor is applicable to projections of total lifetime mortality due to thyroid cancer in a general, exposed population. Omit this factor when considering benign nodules or non-lethal cancers.

Table A.4 gives risk coefficients that are considered to be applicable to the population of the U.S. for mean thyroidal doses ranging from 0.06 to 15 Gy. If the risk coefficients shown in Table A.4 are applied to the general population with an average of 41 remaining years at risk, then the lifetime incidence of fatal thyroid cancer would be 7 to 8 cases per 10^4 persons per Gy following exposure to external irradiation, for a population comprised of equal proportions of males and females and of adults and children. The estimate is concordant with earlier lifetime projections from the UNSCEAR (1977) report (5 to 15 cases), the ICRP (1977) report (5 cases) and the BEIR (1980) report (6 to 18 cases) for similar exposures.

A.6 Chronic Lymphocytic Thyroiditis

A.6.1 Following External X-irradiation in Childhood

De Groot *et al.* (1983) examined a highly selected group of 416 subjects referred because of a history of childhood irradiation and suspected thyroid disease. Serologic testing for antithyroid autoantibodies revealed that 20% were positive for antimicrosomal antibodies and that 9% were positive for antithyroglobulin antibodies. Although no specific control data were included in that report, the statement was made that the presence of positive antibodies in the patients was "more common" than expected. Data were also available regarding clinical findings suggestive of chronic thyroiditis in 319 subjects with an abnormal thyroid examination but no known thyroid cancer: Finely irregular or lobulated glands were found in 44/319 (13.8%) and single or multinodular glands were found in 70/319 (21.9%). In the 113/416 subjects who underwent thyroid surgery, 14/113 (12.4%) had a primary diagnosis of chronic thyroiditis. These findings suggest that chronic thyroiditis occurred at least 12.4% of the time in this highly selected population exposed to a mean thyroidal dose of 4.51 Gy at mean age 7.1 years and examined an average of 26.4 years later. No control group was included for comparison.

Spitalnik and Strauss (1978) reviewed histologic findings in the thyroids of 68 previously irradiated patients who had undergone thyroidectomy and found chronic lymphocytic thyroiditis in 46/68 (68%) compared to no such findings in thyroid glands from age- and gender-matched nonirradiated controls. Okerlund *et al.* (1978) found that 64 of 319 (20%) patients with a history of external radiation therapy to the thyroid area in childhood had clinical stigmata of chronic lymphocytic thyroiditis and positive serologic antithyroid autoantibody tests. Studies of rats (Kotani *et al.*, 1982) exposed to 2-8 Gy of external radiation have shown a 50% incidence of chronic thyroiditis on histologic examination of the thyroid 2-6 weeks postirradiation.

These studies suggest that chronic lymphocytic thyroiditis is a common disease in North Americans receiving external radiation to the thyroid in childhood. Insufficient radiation dosimetric data and a lack of nonirradiated control data in the human populations prohibit meaningful estimates of risk of chronic lymphocytic thyroiditis. Presumably, risk estimates for hypothyroidism and for benign thyroid nodules would encompass the significant clinical manifestations of chronic lymphocytic thyroiditis. For example, in the Michael Reese Hospital series (Frohman *et al.*, 1977) 27/254 operated patients (10.6%) had chronic thyroiditis, but chronic thyroiditis was the primary diagnosis in only 4/254 (1.6%).

Table A.4 Annual Risk in Total and Lethal Excess Thyroid Cancers per 10^4 Persons per Gy of Thyroid Dose for Doses from 0.06 to 15.0 Gy (United States Population)[a]

Source of Irradiation	Persons over age 18 years at exposure				Persons age 18 or less years at exposure			
	Total		Lethal		Total		Lethal	
	Male	Female	Male	Female	Male	Female	Male	Female
^{131}I	0.28	0.56	0.028	0.056	0.56	1.12	0.056	0.112
External x- or gamma rays	0.84	1.68	0.084	0.168	1.68	3.36	0.168	0.336

[a]Based on an absolute risk estimate of 2.5 cases per 10^4 PY per Gy in children exposed to external irradiation in childhood and the considerations shown in Table A.3.

A.6.2 Following Exposure to Irradiation from Nuclear Weapons

Asanao *et al.* (1978) reviewed the results of autopsies performed in Hiroshima and Nagasaki, Japan, between 1954 and 1974. Chronic lymphocytic thyroiditis was found in 89/2289 (3.9%) nonexposed people and in 64/1970 (3.3%) irradiated people who had died and undergone autopsy examination during that time. While the overall incidence of chronic thyroiditis increased from 0.2% in 1956 to 4.9% by 1974, the change was the same in both irradiated and nonirradiated subjects. Thus, in the Japanese exposed to atomic irradiation, there did not appear to be any relationship between chronic thyroiditis and radiation exposure.

A.6.3 Following ^{131}I Therapy

McGregor *et al.* (1979) examined the effects of external irradiation on cultured peripheral-blood lymphocytes from patients with chronic lymphocytic thyroiditis. They found a progressive decrease in production of IgG and thyroglobulin antibody as the dose increased; the decrease was virtually complete by 30 Gy. When irradiated cells were mixed and cocultured with nonirradiated cells, there was a marked stimulation of antibody production that appeared to have a threshold at 10 Gy, was maximal between 20 and 30 Gy, and declined after 40 Gy. These data suggest that at external radiation doses of 20 to 30 Gy selective killing of B-cells and suppressor T-cells occurs, leaving a population of helper T-cells that then stimulate antibody production by nonexposed cells. This was postulated to explain previously observed stimulation of antithyroid immunoglobulins following ^{131}I therapy for thyrotoxic Graves' disease. In addition, the observations of Miller *et al.* (1955) reveal histologic evidence of chronic lymphocytic thyroiditis following ^{131}I therapy in the human thyroid gland. Again, insufficient data exist to permit meaningful risk calculations for chronic thyroiditis, *per se.*

A.7 Acute Radiation Thyroiditis

Radiation thyroiditis is used to describe an acute condition occurring within two weeks after the exposure to radiation and characterized by symptoms of inflammation and eventual necrosis of some or all cells in the thyroid gland (Maxon *et al.*, 1977). The symptoms are usually mild and related to local pain and tenderness over the thyroid gland (Beierwalters and Johnson, 1956; Werner and Ingbar, 1971; De Groot and Stanbury, 1971). Rarely significant systemic symptoms have been associated with massive release of stored thyroid hormone (Shafer and Nuttal, 1971; Krishnamurthy and Blahd, 1974). The syndrome generally resolves within two to four weeks.

Clinically evident radiation thyroiditis after acute or fractionated external radiation therapy or accidental exposure to external radiation has not been reported. The absence of such findings may be due to relatively small doses or to dose fractionation permitting recovery.

Beierwalters and Johnson (1956) reported that very mild acute radiation thyroiditis could be found in 4-5% of the patients with thyrotoxicosis who were treated with ^{131}I. The symptoms were so mild that the patients usually had to be questioned carefully in order to establish their presence. More significant symptoms of increased thyrotoxicosis, presumably related to the release of thyroid hormones by radiation thyroiditis, were considered to be unlikely below single oral doses of 13 mCi of ^{131}I or approximately 174 Gy to the thyroid, assuming a mean 45 gram gland weight, a mean uptake of 65% within 24 hours and an

effective half-life of six days.

Segal and associates (1958) evaluated 65 euthyroid patients with severe ischemic heart disease treated by thyroid ablative doses of ^{131}I. Three of the 65 patients (4.6%) died shortly after therapy, with acute radiation thyroiditis as a contributing factor. The estimated dose of thyroid radiation in those three patients, assuming a 20 gram thyroid and a six day effective half-life, would be in the range of 700 to 1250 Gy. Clinically evident acute radiation thyroiditis did not develop in any of the patients who received less than approximately 320 Gy.

Data from the University of Cincinnati suggest that large amounts of ^{131}I (sufficient to deliver estimated doses of more than 2000 Gy) administered for the ablation of residual thyroid tissue after thyroidectomy for thyroid cancer, may induce acute radiation thyroiditis in 90% of such patients. The resulting symptoms were found to be severe in two of 57 patients (3.5%) so treated (Maxon *et al.*, 1977).

On the basis of these observation, clinically significant acute radiation thyroiditis would seem to be highly unlikely at radiation doses below 200 Gy from ^{131}I. In an additional 5% of exposed persons, thyroiditis would be estimated to develop for each 100 Gy increment above the apparent 200 Gy threshold.

A.8 Benign Thyroid Nodules

A.8.1 Following External Radiotherapy in Childhood

Shore (1980) reported a predominantly linear dose-response for benign thyroid nodules and has observed a longer minimum induction period for benign nodules than for thyroid cancer. A similar observation has been reported for a different population by De Groot *et al.* (1983). The observations by these two groups indicate a minimum induction period for benign thyroid nodules of 10 years, a value which will be used in this report. A summary of the major North American Studies of benign nodules following external radiation exposure is shown in Table A.5.

The composition of the irradiated population by ethnic background and gender has been shown earlier (Table A.2). In the Rochester, New York, group (Woodard, 1980), the previously observed apparent increase in risk for Jews for thyroid cancer was less apparent for benign nodules with a relative risk for Jews/nonJews of 1.75, although the difference was no longer significant. Women appeared to remain at about 2-3 times the risk of men with a female/male ratio of absolute risk of about 2.6.

These findings in North America are similar to those noted in the Israeli *Tinea capitis* studies (Ron and Modan, 1984) in which approximately 10 excess cases of benign thyroid enlargement were found in 10,842 subjects at a mean of 22.8 years after thyroid doses of about 0.09 Gy. Assuming a minimum induction period of 10 years, the resultant absolute risk of benign thyroid enlargement would be about 8 cases per 10^4 PY per Gy. Again, women appeared to be at higher risk than men.

Table A.5 Benign Thyroid Nodules Following External Radiation Therapy to the Head and Neck for Benign Disease in Childhood in the United States

Source	Number Irradiated	Excess Cases of Benign Thyroid Nodules[a]	Mean Years at Risk[b]	Mean Thyroidal Dose (Gy)	PY·Gy at Risk[b]
Harley, et al. (1976) and Shore, et al. (1976)	2,215	10	10	0.06	1329
Woodard, (1980)	2,872	71	22	1.19	75189
Maxon, et al. (1980)	1,266	12	11.5	2.90	42221
Frohman et al. (1977)	1,476	218[c]	18	8.08	214669
Pooled Data	7,829	311	16.2[d]	2.45[d]	333408

[a] Clinically evident disease
[b] Assuming a minimum induction period of 10 years
[c] Based on primary surgical findings of 160 benign thyroid lesions in 254 operated cases with known results and extrapolated to 402/1476 for whom surgical therapy was recommended minus an estimated 35 expected cases in a non-irradiated population of similar age. In 39% of their 254 operated cases, more than 1 diagnosis was present. These analyses are based on the primary diagnosis as determined surgically and histologically.
[d] Weighted average

A.8.2 Following Exposure to Radiation from Mixed External Gamma Irradiation and Internally Absorbed Radionuclides (The Marshallese)

Following the exposure of 251 natives in the Marshall Islands to atomic fallout in 1954, an excess number of benign nodules has been noted over 18 years of follow-up (Lessard, 1983). The data are difficult to use for risk estimates because of the high prevalence of at least biochemical hypothyroidism (wherein high thyroid stimulating hormone [TSH] levels would be expected to stimulate nodule formation in nonsterilized tissue), the effects of intervening thyroid hormonal and/or surgical therapy in some subjects (wherein nodule formation might be decreased), and because of wide variations in radiation dose among the small population. In spite of these limitations, the data do appear to provide some insight into the relationship between age at exposure and the development of benign nodules. Compared to people over the age of 18 years at exposure, the approximate risk per Gy per year for benign nodules was about 2.5 times greater in subjects under the age of 18 years at exposure and was about 5 times greater for those exposed *in utero* (Lessard *et al.*, 1983).

A.8.3 Following Exposure to ^{131}I: Animal Studies

For the production of thyroid adenomas in rats at doses of from one to tens of Gy, ^{131}I has been shown to be several times less effective than x-irradiation (Lee, *et al.*, 1982). At lower doses, ^{131}I and x-rays were found to be of similar effectiveness.

Diverse studies on animals of other noncancerous effects in thyroid glands indicate that there are definite differences in the effectiveness of ^{131}I and external irradiation. Most of them have utilized doses, particularly from ^{131}I, that were in the range of tens of Gy and that probably resulted in cellular changes and cell killing (Table A.6).

For example, in sheep thyroid glands exposed to up to 3000 R from x-irradiation or up to 900 Gy from ^{131}I, histologic changes in the thyroids suggested that ^{131}I was about 1/20 as effective as x-rays for the same extent of tissue injury (McClellan *et al.*, 1963). In mice, the inhibition of goitrogenic stimulation was used as the measure of radiation effect, and indicated ^{131}I to be 1/4 to 1/2 as effective as x-irradiation, based on doses of 10-15 Gy from x-ray and 10-140 Gy from ^{131}I (Walinder *et al.*, 1971). The inhibition of age dependent thyroid growth by irradiation was interpreted to show ^{131}I to be 1/10 to 1/5 as effective (Walinder and Sjoden, 1972), where doses were 1.8 Gy from x-rays and 15-20 Gy from ^{131}I.

In a larger study with rats, Grieg *et al.* (1970) examined the effects on inhibition of goitrogenic stimulation of radiation doses that ranged from 1 to 18 Gy from x-rays and from 5.3 to 510 Gy from ^{131}I (1.25 to 120 μCi). At the higher end of the dose range, the same level of response indicated that ^{131}I had a relative effectiveness of roughly 1/15 to 1/30 compared to x-rays. At the lowest dose, the relative effectiveness was higher, about 1/5.

These results suggest that the effectiveness of ^{131}I relative to x-irradiation for noncancerous effects may be dependent on the magnitude of the dose, and that ^{131}I may approach external irradiation in terms of effectiveness at lower doses. Since large and small doses from ^{131}I are delivered over a similar temporal pattern, these results may also reflect differences in dose rate. Also, at high doses some of the radiation from ^{131}I may be excessive, or "wasted". At the same time, hypothyroidism resulting from higher thyroidal doses will result in elevated levels of TSH, which may in turn be a promoter for carcinogenesis in irradiated cells. Prinz *et al.* (1982) showed a direct correlation between elevated TSH levels and the presence of

Table A.6 Benign Thyroid Changes Following Exposure of Animal to ^{131}I or External Radiation

Source	Animal Studied	Endpoint Examined	Approximate Effectiveness of ^{131}I/External X-irradiation on a per-Gy Basis
Lee et al. (1982)	Rats	Adenomas	0.4 - 1.0
Grieg et al. (1970)	Rats	Inhibition of Goiter Formation	0.03 - 0.2
McClellan et al. (1963)	Sheep	Histopathologic Change	0.05
Walinder et al. (1971)	Mice	Inhibition of Goiter Formation	0.1 - 0.2

thyroid cancer in rats receiving high doses (approximately 70 Gy from 40 μCi) of ^{131}I. Lu and associates (1973) suggested a relationship between changes in TSH levels and thyroidal carcinogenesis in dogs exposed to high dose x-irradiation.

A.8.4 Summary of Risk of Benign Thyroid Nodules Following Exposure to Ionizing Irradiation

The absolute risk of benign thyroid nodules following external radiation therapy in childhood is considered to be 9.3 cases per 10^4 PY per Gy. Women are considered to be twice as susceptible as men, and persons over the age of 18 at exposure are considered half as susceptible as those under the age of 18 at exposure. ^{131}I is considered to be about 1/5 as effective as external radiation on a Gy-for-Gy basis (Table A.7).

A.9 Hypothyroidism

Hypothyroidism is a metabolic state resulting from insufficient amounts of thyroid hormone for normal physiologic function. In its more advanced form, hypothyroidism may result in mental sluggishness, fluid retention, muscle cramps, and a generalized decrease in most bodily functions. The symptoms are readily treated with oral doses of thyroid hormone.

Evidence that hypothyroidism may be induced by radiation exposure comes from many sources. Data from high dose ($\geq$ 20 Gy) external radiation therapy and from high dose ($\geq$ 20 Gy) ^{131}I therapy are reviewed below as a basis for evaluating the risk of hypothyroidism as a function of the dose received.

A.9.1 Following High Dose (> 20 Gy) External Radiation Therapy

In evaluating 95 patients at a mean of 19 years after an average dose of 30 Gy of external radiation to the thyroid in childhood, Kaplan *et al.* (1983) found functional thyroid damage manifested as biochemical hypothyroidism in 42 subjects. If one assumes that, at such high dose levels, functional damage begins soon after the exposure and that the spontaneous rate of clinical hypothyroidism for this group is about 0.6% based on a 0.02% per year spontaneous incidence (Maxon *et al.*, 1977), then no more than 1 case would be expected, yielding an approximate absolute risk of hypothyroidism in 7.6 cases per 10^4 PY per Gy per year after exposure. Because the study focussed on prevalence, the dynamics of risk over time are not clear.

A.9.2 Following High Dose (> 20 Gy) ^{131}I Therapy

Since Graves' disease involves significant morbidity and risk of mortality to the untreated patient, there are no large studies of the natural history of the disease without some form of therapeutic intervention. At the same time, patients with Graves' disease constitute the largest group of people exposed to high dose ^{131}I radiation. In addition, more accurate follow-up and radiation dosimetry data are available on this group of patients than on any other large group exposed solely to ^{131}I. If a reasonable estimate of spontaneous hypothyroidism could be obtained for patients with Graves' disease, then it could be used to normalize the experience of patients with Graves' disease exposed to ^{131}I and thus allow estimation

Table A.7 Annual Risk of Excess Benign Thyroid Nodules per 10^4 Persons per Gy of Thyroid Dose for Doses from 0.06 to 15.0 Gy (United States Population)[a]

Source of Irradiation	Persons Over Age 18 Years at Exposure		Persons Age 18 or Less Years at Exposure	
	Male	Female	Male	Female
^{131}I	0.6	1.2	1.2	2.5
External X or Gamma Rays	3.1	6.2	6.2	12.4

[a]Based on an absolute risk estimate of 9.3 cases per 10^4 persons per Gy per year in children exposed to external irradiation in childhood and the considerations shown in Table A.3.

of the radiation effects alone on the thyroid gland.

In the Cooperative Thyrotoxicosis Follow-up Study (Becker *et al.*, 1971), data were collected on 5221 patients with Graves' disease who were treated with surgery. The constant slope of curves relating the years after treatment to the cumulative probability of becoming hypothyroid following surgical therapy suggests that after the first two years this constant increment in the prevalence of hypothyroidism might be due to ongoing factors related to the underlying disease state rather than to changes initially following surgical therapy. These factors could include autoimmune destruction of the residual thyroid tissue, the effects of various thyroid stimulators, and possibly other changes that are not fully appreciated. The slope of the curves suggests that each year 0.7% of the population with Graves' disease would become hypothyroid, probably on the basis of these factors rather than on the basis of surgery alone.

In support of this hypothesis are the unique long-term follow-up data of Wood and Maloof (1975) on adult patients treated with antithyroid drugs for Graves' disease. Their report indicates that two of 15 such patients became clinically hypothyroid by 20 years following the initiation of therapy, suggesting that the incidence of spontaneous hypothyroidism in patients with Graves' disease should be about 0.7% per year.

The figure of 0.7% per year probability of hypothyroidism has been used in the current report to estimate the rate of spontaneous hypothyroidism in a population with Graves' disease (Maxon *et al.*, 1977).

In the data presented by Becker *et al.* (1971), 6000 patients were treated with only a single dose of ^{131}I. The cumulative probability of becoming hypothyroid was related to the amount of ^{131}I retained by the thyroid gland in terms of microcuries per estimated gram of initial thyroid weight. These data have been used in calculating the radiation dose to the thyroid by multiplying the thyroidal concentration of ^{131}I by 0.91 Gy per μCi per gram. This calculation assumes a six day effective half life (Maxon *et al.*, 1981).

The five year follow-up data were selected for analysis because there was not a statistically significant difference in the slopes of the curves from that point on and because optimal numbers of patients were still included (Maxon *et al.*, 1977). A cumulative probability of 3.5% (0.7% per year times five years) for spontaneous hypothyroidism in Graves' disease was subtracted from the ^{131}I cumulative probability dose response curves at this five year period to result in an estimate of the probability of hypothyroidism from ^{131}I exposure alone (Maxon *et al.*, 1977). A curve of incidence versus time shows a rapid increase within the first two years after exposure, followed by a period of less rapid increase. The data appear to approach asymptotically the lifetime incidence, however they are not strong enough to serve as a basis for detailed projections of the risk as a function of time since exposure.

The results (Maxon *et al.*, 1977) show a strong linear correlation between the radiation dose to the thyroid from ^{131}I and the probability of hypothyroidism above a lower limit of approximately 25 Gy — the lowest dose at which data were available in the study by Becker *et al.* (1971). A dose of approximately 600 Gy would be projected to render all subjects hypothyroid by five years after exposure.

In the Cooperative Thyrotoxicosis Follow-up Study, the bias of age at the time of diagnosis on choice of therapy and the frequency of follow-up was so strong at certain of the participating medical centers that it prevented any final conclusions regarding the relationships

between age at exposure to ^{131}I and outcome. Nevertheless, every analysis the investigators performed failed to demonstrate a relationship between age at exposure and subsequent hypothyroidism (Maxon *et al.*, 1977).

Euthyroid adult patients without thyrotoxicosis were occasionally treated with ^{131}I for cardiac disease in the past. Assuming a 20 gram thyroid gland with a six day effective half-life, Chapman (1975) found that 22 of 28 (80%) such patients were clinically hypothyroid five years after therapy with a calculated mean dose of 320 Gy from ^{131}I. Segal *et al.* (1958) and Goolden and Davey (1963) found that total ablation of the thyroid with associated hypothyroidism could be obtained within the first year after exposure to radioiodine therapy in euthyroid cardiac patients but that it always required amounts retrospectively found to deliver at least 270 Gy based on the dosimetric assumptions cited for Chapman (1975) above. Similar calculations based on the data of Segal *et al.* (1958) also indicate that a mean dose of about 490 Gy was required to render 65 euthyroid adult cardiac patients hypothyroid by ^{131}I therapy.

A.9.3 Summary of Risk of Hypothyroidism Due to Ionizing Radiation

The absolute risk of clinical hypothyroidism after treatment of Graves' disease with ^{131}I in doses greater than 25 Gy would appear to be 4.4 cases per 10^4 PY per Gy. Data from ^{131}I treated cardiac patients suggest that this figure may be applied to the general population. Although the absolute risk of hypothyroidism from ^{131}I at high doses (> 20 Gy) appears to be about 1/2 of the value for external radiation at similarly high doses, the data are not considered sufficient to consider this more than a very rough approximation.

Based on animal studies, ^{131}I would appear to be about 1/5 as effective as external radiation on a Gy-for-Gy basis in the induction of functional changes to the thyroid. For this report, ^{131}I is considered to be 1/5 as effective as external radiation in the induction of hypothyroidism.

Because of the lack of data other than doses in the region of several to tens of Gy and because of the high probability that at such doses all cases of hypothyroidism would become apparent within a relatively few years after exposure, it is not considered appropriate to calculate risk on the lifetime basis of 41 years at risk. It appears from the human data that doses of 600 Gy from ^{131}I would have a very high probability of rendering 100% of the population hypothyroid by 5 years postexposure. This would correspond to 120 Gy from external x-irradiation, using a 1/5 factor for ^{131}I. Thus the actual lifetime risk of hypothyroidism could be expressed as ($[1 \times 10^6$ cases$]/[600$ Gy per case$]$) or 16.7 cases per 10^4 persons per Gy at doses up to 600 Gy following ^{131}I exposure. For external radiation the risk would be 83.3 cases per 10^4 persons per Gy at doses up to 120 Gy following external gamma or x-ray exposure. It must also be noted that hypothyroidism is almost certainly a threshold effect, but there are no data adequate to determine the exact threshold.

The children exposed to external radiation therapy in Cincinnati (Maxon *et al.*, 1980) had no historical evidence of an increased risk of hypothyroidism at mean thyroidal doses of 2.9 Gy. In the Marshallese exposed to atomic fallout with characteristics more like external x-ray exposure than ^{131}I exposure and with mean thyroidal doses of approximately 7.9 Gy, there has been a definite increase in the incidence of at least biochemical hypothyroidism as

manifest by increased serum TSH concentrations (Conard *et al.*, 1980; Lessard, 1983). Until further data become available, a threshold of 2.0 Gy from external radiation will be assumed for clinical hypothyroidism.

Based on these considerations, a model for hypothyroidism following thyroidal irradiation can be constructed as shown in Table A.8.

Table A.8 Lifetime Risk of Hypothyroidism Following External Radiation or ^{131}I Exposure[a]

Source of Irradiation	Range of Doses		Risk (Cases Per 10^4 Persons Per Gy)
	Threshold (Gy)	Applicable Upper Limit (Gy)	
^{131}I	10	600	17
External x- or gamma radiation	2	120	83

[a]Because hypothryoidism due to high dose irradiation would be expected to occur over an ill-defined but limited time period and because there are no data which permit calculation of a meaningful annual risk for an indefinite time, data are presented in terms of lifetime risk.

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Appendix A.A

COMMENTS ON ABSOLUTE VS. RELATIVE RISK ESTIMATES

One problem of any risk estimate procedure is that of projecting risk beyond the period of observation. There are no human data to suggest that the incidence of radiation associated thyroid cancer will continue to increase in a linear manner indefinitely. Indeed there are very preliminary indicators that the incidence may decrease after about 40 to 50 years. For thyroid cancer, there is the additional difficulty that estimates of effects are based almost entirely on persons exposed to external x-irradiation early in childhood. Finally there are apparent differences in the so-called "natural incidence" in groups of widely differing heritage. It was the judgment of the group preparing this report that a traditional relative risk calculation for thyroid cancer might be particularly susceptible to these factors, with resultant serious overestimations of risk. At the same time, it was obvious that while a traditional absolute risk calculation might be less affected by these factors, risk was clearly not a single linear function.

To help test this hypothesis, Ethel S. Gilbert, staff scientist in the statistics section of Batelle Pacific Northwest Laboratories was asked to evaluate the data. She developed a life table analysis for the United States based on the 1978 age distribution in the United States and data from the SEER Registries to estimate spontaneous cases (Table A.A.1). Using the data in Table A.A.1, she then calculated the number of excess external radiation associated with thyroid cancers that would be predicted by an absolute model using risk estimates of 2.5 and 1.25 cases per 10^4 PY per Gy (depending on age). This resulted in a lifetime projection of 72.1 cases per 10^4 persons per Gy. The specific risk estimates from Table A.4 in this report would project 76.9 cases per 10^4 persons per Gy for a population equally divided between males and females and between adults and children with an average of 41 years at risk. She also prepared a lifetime estimate based on a relative risk model in which it was assumed that the actual observed number of excess cases over the approximate period of observation of 5 to 30 years post exposure was the same for both relative and absolute risk models for each of the two age groups. The resultant lifetime estimate of excess cancers was 86.6 cases per 10^4 persons per Gy. The relative risks were 540% per Gy for people exposed at age less than 20 years and 180% per Gy for people 20 years of age or older at the time of exposure. These relative risks contrasted sharply to other estimates based on single studies of children exposed early in life. (Data from Shore [1980], for example, suggest a relative risk of 2500% per Gy, although they did not specifically advocate such a number for purposes such as those in this report.)

For these and other reasons stated in the report, the authors consider the proposed specific risk estimate model to represent a practical compromise for use until better data become available.

Table A.A.1 Basic Data for Calculating Lifetime Risks of Thyroid Based on the 1978 Age Distribution of the U.S. Population and 1978 Life Tables for the U.S.

	Parameter	Age at Exposure	
		0-19	≥20
(1)	Proportion of population	0.328	0.672
(2)	Average life expectancy (years) beyond a 5-year minimum induction	59.0	28.2
(3)	Person-years contributed by age group in total population (1) x (2) x population	19.35×10^6	18.95×10^6
(4)	Spontaneous cases per 10^6 of thyroid cancer expected beyond a 5-year minimum induction	3534.5	1985.9
(5)	Spontaneous cases contributed by age group in total population (1) x (4)	1159.3	1334.5

Appendix A.B

TIME OF DEATH DUE TO THYROID CANCER IN IRRADIATED PATIENTS

The times at which deaths from papillary and follicular thyroid cancer occur may be important in predicting the course and outcome for populations of affected people. Two of the largest experiences are those from the Mayo Clinic (McConahey *et al.*, 1981) and the Lahey Clinic (Cady *et al.*, 1976). The Mayo Clinic series included 820 patients with papillary carcinoma and 174 patients with follicular carcinoma treated between 1946 and 1971. The Lahey Clinic series included 423 patients with papillary carcinoma and 178 patients with follicular carcinoma treated between 1931 and 1970. The distribution of deaths due to thyroid cancer for the 1595 patients in the two populations is shown in Table A.B.1. The proportion of follicular carcinomas (22%) was about twice what would be predicted for radiation-associated thyroid cancers (10%).

If the average values for the percent of deaths during each time interval (Table A.B.1) are weighted according to the projected distributions of death due to each histologic type of thyroid cancer following irradiation (three-fourths due to papillary and one-fourth due to follicular cancer), then an estimate of the time of death due to radiation-associated thyroid cancer may be obtained (Table A.B.2). These approximations are not appropriate for application to individual cases of thyroid cancer. For individuals, factors such as age at diagnosis, gender, size of the primary cancer, extent of invasion or spread at diagnosis, degree of cellular differentiation of the primary cancer, and type of treatment would be important in determining outcome (McConahey *et al.*, 1981; Cady *et al.*, 1976).

Table A.B.1 Time Distribution of Deaths due to Papillary or Follicular Carcinoma of the Thyroid

Time After Diagnosis (Years)	Papillary Carcinoma			Follicular Carcinoma		
	Mayo Clinic	Lahey Clinic	Arithmetic Mean	Mayo Clinic	Lahey Clinic	Arithmetic Mean
0 - 5	40%[a]	48%	44%	53%	49%	51%
6 - 10	30%	14%	22%	7%	27%	17%
11 - 15	--	21%	10.5%	7%	10%	8.5%
16 - 20	--	7%	3.5%	33%	8%	20.5%
21 or more	30%	10%	20%	--	6%	3%

[a]Percent of total lifetime deaths occurring in each time interval.

Table A.B.2 Estimated Time Distribution of Total Deaths Due to Radiation-Associated Thyroid Carcinoma

Time After Diagnosis (Years)	Type of Cancer				
	Papillary	+	Follicular	=	Total[b]
0 - 5	33%[a]		13%		46%
6 - 10	16%		4%		20%
11 - 15	8%		2%		10%
16 - 20	3%		5%		8%
21 or more	15%		1%		16%
	75%		25%		100%

[a]Percent of total lifetime deaths occurring in each time interval.

[b]Distribution of total deaths due to radiation-associated thyroid cancer, regardless of cell type, over each time period.

Appendix B

BASE-LINE DEMOGRAPHIC AND MORTALITY DATA

Table B.1 1980 U.S. Population, All Races[a]

Age	Both Sexes	Male	Female
Total persons	226 545 805	110 053 161	116 492 644
Under 1 year	3 533 692	1 806 338	1 727 354
1 year	3 269 557	1 674 095	1 595 462
2 years	3 223 816	1 648 044	1 575 772
3 years	3 179 441	1 625 693	1 553 748
4 years	3 141 748	1 607 839	1 533 909
5 years	3 162 691	1 618 300	1 544 391
6 years	3 109 095	1 589 501	1 519 594
7 years	3 273 052	1 672 647	1 600 405
8 years	3 394 998	1 735 956	1 659 042
9 years	3 760 120	1 922 676	1 837 444
10 years	3 716 530	1 901 610	1 814 920
11 years	3 580 644	1 828 934	1 751 710
12 years	3 518 982	1 796 333	1 722 649
13 years	3 643 189	1 856 566	1 786 623
14 years	3 782 784	1 932 778	1 850 006
15 years	4 059 898	2 069 726	1 990 172
16 years	4 180 875	2 135 125	2 045 750
17 years	4 223 848	2 160 114	2 063 734
18 years	4 251 779	2 153 292	2 098 487
19 years	4 451 724	2 237 152	2 214 572
20 years	4 387 100	2 200 363	2 186 737
21 years	4 285 763	2 144 501	2 141 262
22 years	4 284 351	2 144 967	2 139 384
23 years	4 199 711	2 096 561	2 103 150
24 years	4 161 779	2 076 839	2 084 940
25 years	4 116 218	2 052 580	2 063 638
26 years	3 977 515	1 978 833	1 998 682
27 years	3 931 620	1 951 928	1 979 692
28 years	3 708 968	1 840 454	1 868 514
29 years	3 786 598	1 881 312	1 905 286
30 years	3 726 525	1 846 502	1 880 023
31 years	3 607 610	1 781 174	1 826 436
32 years	3 712 217	1 833 056	1 879 161
33 years	3 653 921	1 804 683	1 849 238
34 years	2 860 647	1 411 381	1 449 266
35 years	2 902 331	1 430 252	1 472 079
36 years	2 929 040	1 439 277	1 489 763
37 years	2 982 533	1 464 708	1 517 825
38 years	2 598 636	1 272 819	1 325 817
39 years	2 552 762	1 254 453	1 298 309
40 years	2 468 083	1 209 237	1 258 846
41 years	2 375 849	1 164 333	1 211 516
42 years	2 325 572	1 139 469	1 186 103
43 years	2 237 108	1 091 654	1 145 454
44 years	2 262 796	1 103 517	1 159 279
45 years	2 242 318	1 093 845	1 148 473
46 years	2 139 385	1 040 326	1 099 059
47 years	2 222 969	1 077 163	1 145 806
48 years	2 163 709	1 051 506	1 112 203
49 years	2 321 374	1 125 409	1 195 965
50 years	2 347 068	1 134 304	1 212 764
51 years	2 295 077	1 105 801	1 189 276
52 years	2 363 152	1 136 693	1 226 459
53 years	2 337 138	1 119 210	1 217 928
54 years	2 367 597	1 124 662	1 242 935
55 years	2 390 440	1 130 295	1 260 145
56 years	2 329 790	1 102 430	1 227 360
57 years	2 312 737	1 091 620	1 221 117
58 years	2 330 373	1 099 788	1 230 585
59 years	2 251 914	1 057 730	1 194 184
60 years	2 160 937	1 009 976	1 150 961
61 years	2 073 764	963 777	1 109 987
62 years	2 008 093	930 934	1 077 159
63 years	1 931 425	889 124	1 042 301
64 years	1 913 402	876 081	1 037 321
65 years	1 904 641	862 271	1 042 370
66 years	1 813 987	814 405	999 582
67 years	1 763 637	784 377	979 260
68 years	1 678 740	740 110	938 630
69 years	1 621 476	701 792	919 684
70 years	1 516 900	653 456	863 444
71 years	1 439 723	612 074	827 649
72 years	1 371 235	576 737	794 498
73 years	1 261 994	520 827	741 167
74 years	1 208 272	490 453	717 819
75 years	1 111 480	442 991	668 489
76 years	1 028 927	405 546	623 381
77 years	951 774	366 713	585 061
78 years	828 866	314 780	514 086
79 years	872 675	317 631	555 044
80 years	723 049	260 833	462 216
81 years	640 276	224 125	416 151
82 years	566 548	197 006	369 542
83 years	527 982	179 355	348 627
84 years	477 178	157 908	319 270
85 years	412 549	134 970	277 579
86 years	350 655	111 863	238 792
87 years	306 906	95 624	211 282
88 years	236 314	71 873	164 441
89 years	213 778	62 855	150 923
90 to 94 years	556 592	159 077	397 515
95 to 99 years	131 079	34 961	96 118
100 years and over	32 194	10 302	21 892
Median	30.0	28.8	31.2

[a]From General Population Characteristics, United States Summary, Census of Population, U.S. Department of Commerce, Bureau of the Census, 1980; Table 41.

Table B.2 Number of Survivors, Out of 100,000 Born Alive, United States, 1978

AGE	TOTAL		
	BOTH SEXES	MALE	FEMALE
0	100,000	100,000	100,000
1	98,621	98,473	98,776
2	98,528	98,367	98,698
3	98,456	98,286	98,635
4	98,399	98,222	98,584
5	98,351	98,169	98,542
6	98,310	98,123	98,507
7	98,273	98,081	98,477
8	98,240	98,042	98,450
9	98,211	98,008	98,426
10	98,186	97,978	98,405
11	98,163	97,952	98,386
12	98,140	97,925	98,367
13	98,112	97,891	98,345
14	98,072	97,839	98,318
15	98,017	97,764	98,284
16	97,944	97,662	98,242
17	97,855	97,536	98,191
18	97,752	97,389	98,134
19	97,640	97,226	98,074
20	97,521	97,051	98,012
21	97,396	96,866	97,949
22	97,266	96,670	97,884
23	97,132	96,469	97,818
24	96,998	96,267	97,751
25	96,865	96,069	97,684
26	96,735	95,877	97,615
27	96,607	95,690	97,546
28	96,481	95,508	97,475
29	96,355	95,328	97,403
30	96,229	95,150	97,329
31	96,102	94,973	97,252
32	95,973	94,796	97,172
33	95,840	94,616	97,087
34	95,702	94,430	96,997
35	95,557	94,234	96,901
36	95,403	94,027	96,799
37	95,238	93,807	96,688
38	95,060	93,571	96,567
39	94,867	93,318	96,433
40	94,657	93,045	96,284
41	94,427	92,750	96,118
42	94,176	92,429	95,934
43	93,900	92,089	95,731
44	93,598	91,699	95,507
45	93,268	91,283	95,262
46	92,907	90,829	94,993
47	92,512	90,334	94,698
48	92,080	89,792	94,376
49	91,608	89,197	94,026
50	91,091	88,543	93,647
51	90,526	87,824	93,235
52	89,910	87,037	92,788
53	89,243	86,184	92,306
54	88,527	85,268	91,788
55	87,761	84,289	91,234
56	86,945	83,249	90,643
57	86,075	82,141	90,010
58	85,135	80,947	89,326
59	84,108	79,643	88,579
60	82,981	78,213	87,759
61	81,744	76,648	86,858
62	80,401	74,953	85,876
63	78,966	73,144	84,824
64	77,462	71,246	83,720
65	75,902	69,277	82,572
66	74,292	67,244	81,381
67	72,621	65,141	80,134
68	70,873	62,954	78,814
69	69,024	60,664	77,396
70	67,056	58,259	75,862
71	64,971	55,742	74,208
72	62,772	53,126	72,431
73	60,449	50,413	70,507
74	57,992	47,608	68,410
75	55,397	44,720	66,121
76	52,671	41,764	63,638
77	49,828	38,760	60,971
78	46,890	35,733	58,138
79	43,882	32,710	55,163
80	40,832	29,721	52,070
81	37,766	26,797	48,881
82	34,712	23,973	45,615
83	31,696	21,284	42,291
84	28,747	18,767	38,923
85	25,891	16,462	35,524

[a]Life Tables, Vital Statistics of the United States, 1978 Volume II - Section 5; Table 5.2

Table B.3 Fraction of U.S. Population by Age, All Races

Age Interval	Total 1980[a] (226,545,805)	Female 1980[a] (116,492,644)	Age Interval	Total[b]	Female[b]
0-4	0.07215	0.0685	0-9	0.147	0.141
5-9	0.07371	0.0700			
10-14	0.08051	0.0800	10-19	0.181	0.174
15-19	0.09342	0.0894			
20-24	0.09409	0.0914	20-29	0.175	0.172
25-29	0.08616	0.0842			
30-34	0.07750	0.0763	30-39	0.133	0.132
35-39	0.06163	0.0610			
40-44	0.05150	0.0512	40-99	0.363	0.385
45-49	0.04894	0.0489			
50-54	0.05160	0.0522			
55-59	0.05126	0.0526			
60-64	0.04452	0.0465			
65-69	0.03875	0.0419			
70-74	0.02999	0.0338			
75-79	0.02114	0.0253			
80-84	0.01295	0.0164			
85-89	0.00670	0.0089			
90-94	0.00245	0.0034			
95-99	0.00057	0.0008			

[a] From General Population Characteristics, United States Summary, Census of Population, U.S. Department of Commerce, Bureau of the Census, 1980; Table 41

[b] From Chapter 4, Table 4.10; based on U.S. population, 1978

Table B.4. 1978 Cancer Mortality Rates (Deaths/Year per 100,000 Population)[a]

Age	All Cancer Excluding * Group[b]	Gastroin-Testinal	Lung Cancer	Breast Cancer	Other Cancer[c]
0-4	3.1	0.2	0	-	2.9
5-9	2.2	0.1	0	-	2.1
10-14	1.8	0.1	0	-	1.7
15-19	2.9	0.2	0	0	2.7
20-24	4.5	0.4	0.1	0.2	3.9
25-29	7.8	1.0	0.3	1.2	5.9
30-34	14.7	2.4	1.3	5.6	8.2
35-39	28.3	5.2	4.8	11.7	12.3
40-44	62.3	11.8	15.1	22.9	23.6
45-49	124.1	25.0	36.2	41.4	41.6
50-54	219.5	48.1	70.6	60.1	69.5
55-59	333.1	79.1	110.2	75.9	103.9
60-64	505.6	133.1	166.4	91.4	157.1
65-69	633.4	184.8	201.3	89.9	196.8
70-74	829.6	266.8	238.2	110.7	260.0
75-79	1041.1	376.3	245.0	128.4	340.8
80-84	1171.4	467.4	218.3	139.9	394.4
85-89	1178.5	513.3	147.1	157.2	408.6

[a]Source: Vital Statistics of the U.S., 1978

[b]* Group: Leukemia, Skin, Bone, Prostate, Thyroid

[c]Excluding * Group and Gastrointestinal, Lung, and Breast

Table B.5. 1973-1977 Cancer Incidence Rates (New Cases/Year per 100,000 Population)[a]

Age	All Cancer Excluding * Group[b]	Gastrointestinal Cancer	Lung Cancer	Breast Cancer (Females)	Other Cancer[c]
0-4	10.2	0.7	0	-	9.5
5-9	5.8	0.2	0	-	5.6
10-14	6.5	0.3	0.1	-	6.1
15-19	11.5	0.5	0.2	0.2	10.7
20-24	20.4	1.3	0.2	1.1	18.3
25-29	33.2	2.4	0.7	8.3	25.9
30-34	55.4	5.5	2.3	26.7	34.1
35-39	93.5	11.9	7.1	57.2	45.3
40-44	170.4	24.9	20.4	106.2	70.6
45-49	300.6	50.2	47.7	173.8	113.7
50-54	457.3	89.4	79.8	195.9	187.2
55-59	682.1	155.5	130.2	228.9	277.6
60-64	910.5	240.5	185.6	251.2	351.8
65-69	1163.4	351.2	235.5	282.9	420.1
70-74	1399.4	475.2	258.5	302.0	489.6
75-79	1646.9	617.9	255.9	338.0	564.4
80-84	1733.3	708.9	211.4	350.0	586.2
85-89	1831.0	795.6	166.0	376.3	611.3

[a]Source: Cancer Incidence and Mortality in the United States, 1973-77 (SEER)

[b]* Group: Leukemia, Skin, Bone, Prostate, Thyroid

[c]Excluding * Group and Gastrointestinal, Lung, and Breast

Table B.6 1978 U.S. Age-Specific Population and Births

Age (yr)	White Males		White Females		Births[c]
	Population[a]	$_nL_x$[b]	Population[a]	$_nL_x$[b]	
0	7182	98825	6833	99072	0
1	27145	394014	25814	395283	0
5	37868	491440	36124	493314	0
10	41955	490604	40116	492749	29
15	47690	488360	46211	491793	2418
20	46116	484072	45597	490325	5819
25	41170	479688	41033	488818	5472
30	36612	475820	36723	487151	2552
35	29769	471426	30643	484938	648
40	25740	465182	26583	481430	111
45	25931	455217	26912	475598	6
50	27007	439187	28783	466511	0
55	25624	414767	27908	452973	0
60	21282	378308	24028	432730	0
65	18012	328269	22539	404187	0
70	12944	265672	17890	364287	0
75	7882	192039	12488	305546	0
80	4675	117620	8661	226259	0
85	3233	89129	7278	246257	0

[a]Number of white males or white females out of 1,000,000.

[b]Stationary population: Number of white males or white females in each age group (100,000 annual births). Vital Sataistics of the United States, 1978

[c]Births per year per 10^6 persons. Births have been increased by a factor of 1.25 from the 1978 U.S. figures to establish a stable population.

Table B.7 Live Births By Age of Mother, All races, United States, 1980

Age of Mother	Live Births[a] U.S. 1980
All Ages	3,612,258
15	10,169
15-19	552,161
20-24	1,226,200
25-29	1,108,291
30-34	550,354
35-39	140,793
40-44	23,090
45-49	1,200

[a]Source: Monthly Vital Statistics Report, Vol. 31, No. 8, Supplement, November 30, 1982

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Laurel, MD 20707
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9G (Tech Only), RH, RE, 9E

USNRC (28)
Division of Risk Analysis and Operations
Washington, DC 20555
Attn: M. Cunningham
J. Glynn
T. Margulies
J. Martin (25)

USNRC (2)
Health Effects Branch
1130 SS
Washington, D. C. 20555
Attn: S. S. Yaniv
J. Puskin

USNRC (3)
Section B, M/S P-822
Accident Evaluation Branch
Washington, DC 20555
Attn: L. Soffer
L. Bell
J. Hulman

USNRC
Division of Safety Technology
M/S 216
Washington, DC 20555
Attn: S. Acharya

John Abbott
National Institutes of Health
Building 1, Room 137
Bethesda, MD 20205

Seymour Abrahamson, Ph.D. (2)
Department of Zoology
University of Wisconsin
Madison, WI 53706

SAIC (2)
1710 Goodridge Drive
P. O. Box 1303
McLean, VA 22102
Attn: D. C. Aldrich
R. Blond

J. Allison
Embassy of Australia
Office of the Counsellor (Atomic Energy)
1601 Massachusetts Avenue
Washington, DC 20036

Prof. Dr. Dr. J. Ammon
Abteing Radiobiologie Der
Medizinischen Fakultaet
Phein.-Westf. Techn. Hochschule
Goethestr. 2-29
D-5100 Aachen
FEDERAL REPUBLIC OF GERMANY

David Auton
Defense Nuclear Agency
Washington, DC 20305

John A. Auxier
Oak Ridge National Laboratory
P.O. Box X
Oak Ridge, TN 37830

William J. Bair, Ph.D.
Manager, Environmental, Health and
Safety Research Program
Battelle Pacific Northwest Laboratories
Richland, WA 99352

Ioannis G. Bartzis
Greek Atomic Energy Commission
Nuclear Research Center Demokritos
Aghia Paraskevi
153 10 Attikis
GREECE

Prof. Dr. Anthony Bayer, INR
Kerforschungszentrum Karlsruhe G.m.b.H.
Postfach 3640
D-7500 Karlsruhe 1
FEDERAL REPUBLIC OF GERMANY

Gilbert W. Beebe
Clinical Epidemiology Branch
National Cancer Institute
Landow Building, Room 8C41
Bethesda, MD 20205

Thomas Bell
Armed Forces Radiobiology
Research Institute
Bethesda, MD 20014

Michael A. Bender, Ph.D. (2)
Medical Department
Brookhaven National Laboratory
Upton, Long Island, NY 11973

David W. Bensen
Program Manager for Nuclear Hazards
National Security Office of
Mitigation and Research
Federal Emergency Management
Agency
1725 I Street, N.W., Room 909
Washington, DC 20472

Jan Beyea
National Audubon Society
950 Third Ave.
New York, NY 10022

Victor P. Bond, M.D., Ph.D.
Associate Director for Biology, Medicine,
Environment and Safety
Brookhaven National Laboratory
Upton, Long Island, NY 11973

Steven A. Book, Ph.D. (2)
Laboratory for Energy-Related
Health Research
University of California-Davis
Davis, CA 95616

Edward Branagen, Jr.
Nuclear Regulatory Commission
Washington, DC 20555

R. Chiacchierimi
Bureau of Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Carla Brofferio
Comitato Nazionale per l'Energia Nucleare
Viale Regina Margherita, 125
Casella Postale N. 2358
I-00100 Roma A. D.
ITALY

Stephen L. Brown
Commission of Life Sciences
NRC/NAS
2101 Constitution Ave NW
Washington, DC 20418

Mr. Robert Budnitz
Future Resource, Associates
200 Center Street
Suite 418
Berkely, CA 94704

C. Ralph Buncher, Sc.D. (2)
Department of Environmental Health
G11 William B. Wherry Hall
University of Cincinnati
Mail Location #183
Cincinnati, OH 45276-0183

Klaus Burkart
Institut fur Neutronenphysik und
Reaktortechnik (INR)
Kernforschungszentrum Karlsruhe G.m.b.H.
Postfach 3640
D-7500 Karlsruhe 1
FEDERAL REPUBLIC OF GERMANY

Surgeon Captain Bob Carmichael
Head of Defence Radiological
Protection Service
c/o Institute of Naval Medicine
Alverstoke
Gosport
Hants P012 2DL
ENGLAND

S. Chakraborty
Abtielung fur die sicherheit der Kernanlagen
Eidgenossisches Amt fur Energiewirtschaft
CH-5303
Wurenlingen
SWITZERLAND

Dr. M. W. Charles
Central Electricity Generating Board
Berkeley Nuclear Laboratories
Berkeley, Gloucestershire, GL13 9PB
ENGLAND

Alistair D. Christie
Deputy Director, Air Quality and
Inter-Environmental Research Branch
Environment Canada
Atmospheric Environment Service
4905 Dufferin Street
City of North York, Downsview
Ontario, M3H 5T4
CANADA

Thomas B. Cochran, Ph.D.
Natural Resources Defense Council
1725 I Street N.W.
Suite 600
Washington, DC 20006

Douglas W. Cooper (2)
T. J. Watson Research Center
P. O. Box 218
Yorktown Heights, NY 10598

M. Crick
National Radiological Protection Board
Chilton
Didcot
Oxon OX11 ORQ
UNITED KINGDOM

James F. Crow, Ph.D.
Genetics Department
University of Wisconsin
Madison, WI 53706

Richard C. Cuddihy, Ph.D.
Inhalation Toxicology Research Institute
Lovelace Institute
Albuquerque, NM 87185

L. Joe Deal
EP-34 GTN
U. S. Department of Energy
Washington, DC 20545

J. A. Dennis
c/o Alice Coulter
British Embassy
UKAEA
3100 Massachusetts Ave., N.W.
Washington, DC 20008

Carter Denniston, Ph.D. (2)
Department of Genetics
University of Wisconsin
Madison, WI 53706

Lennart Devell
Studsvik Energiteknik AB
Studsvik
Fack
S-611 82 Nykoping 1
SWEDEN

Robert Devine
Armed Forces Radiobiology
Research Institute
Bethesda, MD 20014

R. Lowry Dobson
University of California
Lawrence Livermore National Laboratory
P.O. Box 808
Livermore, CA 94550

Keith Eckerman, Ph.D.
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830

Berend Th. Eendebak
KEMA Laboratories
Utrechtseweg, 310
Postbus 9035
NL-6800 ET Arnhem
NETHERLANDS

Joachim Ehrhardt, INR (2)
Kerforschungszentrum Karlsruhe G.m.b.H.
Postfach 3640
D-7500 Karlsruhe 1
FEDERAL REPUBLIC OF GERMANY

Prof. John Evans, Sc. D., CIH (25)
Harvard School of Public Health
665 Huntington Avenue
Boston, MA 02115

Jacob I. Fabrikant, M.D., Ph.D.
University of California
School of Medicine
San Francisco, CA 94101

Prof. Dr. T. M. Fliedner
Abteilung Fuer Klinische Physiologie
Universitaet ULM
Oberer Eselsberg M24
D-7900 ULM
FEDERAL REPUBLIC OF GERMANY

Hymer L. Friedell
School of Medicine, Room W144
Case Western Reserve University
2119 Abington Road
Cleveland, OH 44106

R. Michael Fry
Biology Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830

D. Gallego
Departamento De Tecnologia Nuclear
E.T.S. Ingenieros Industriales
Universidad Politecnica
De Madrid
Spain

Carl R. Gerber
Radiation Policy Council
New Executive Office Building
Room 5011
Washington, DC 20503

Ethel Gilbert, Ph.D. (2)
Statistics Section
Battelle Pacific Northwest Laboratories
Richland, WA 99352

Ernest Gilby
Gilby Associates
Nethertoun
Glebelands Road
Knutsford
Cheshire, WA16 9DZ
UNITED KINGDOM

Henry A. Gill, Jr.
GC-23 FORSTL
U. S. Department of Energy
Washington, DC 20585

John W. Gofman
Dept. of Medical Physics
and Bio Physics
102 Donner Laboratory
University of California
Berkeley, CA 94720

Marvin Goldman, Ph.D.
Laboratory for Energy Related
Health Research
University of California, Davis
Davis, CA 94616

Robert Goldsmith
ER-73, GTN
U. S. Department of Energy
Washington, DC 20545

Paul Govaerts
Health Physics Dept.
SCK/CEN
Boeretang 200
B-2400
MOL, BELGIUM

Douglas Grahn
Division of Biological and
Medical Research
Argonne National Laboratory
Argonne, IL 60439

Peter Groer
Institute for Energy Analysis
Oak Ridge Associated Universities
Oak Ridge, TN 37830

R. Gross
Armed Forces Radiobiology
Research Institute
Bethesda, MD 20014

Christina Gyllander
Sothonsvagen 3
611 00 Nykoping
SWEDEN

Fletcher Hahn, D.V.M., Ph.D. (2)
Lovelace Inhalation Toxicology
Research Institute
P. O. Box 5890
Albuquerque, NM 87185

David Harward
AIF
7101 Wisconsin Ave
Bethesda, MD 20814

Geoffrey Harris
Nuclear Safeguards Branch
South of Scotland Electricity Board
Cathcart House
Spean Street
Glsgow G44 4BE
SCOTLAND

Tadashi Hashizume
c/o Dr Takashi Maruyama
National Institute of
Radiobiological Sciences
9-1, Anagawa - chome
Chiba-shi 260
JAPAN

Thomas Haycraft
Defense Nuclear Agency
Washington, DC 20305

Michael Haynes
United Kingdom Atomic Energy Authority
Safety & Reliability Directorate
Wigshaw Lane
Culcheth
Warrington WA3 4NE
UNITED KINGDOM

Vicki Hertzberg, Ph.D. (2)
Department of Environmental Health
G08 William B.Wherry Hall
University of Cincinnati
Mail Location #183
Cincinnati, OH 45267-0183

David G. Hoel
Director of Biometry and
Risk Assessment Program
National Institute of Environmental
and Health Sciences
PO Box 12233
Research Triangle Park, NC 27709

Edward Hofer
Gesellschaft fur Reaktorsicherheit
D-8046 Garching
FEDERAL REPUBLIC OF GERMANY

F. O. Hoffman
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830

Toshimitsu Homma
Dept. of Nuclear Safety Evaluation
Japan Atomic Energy Research Institute
Tokai-mura
Obaraki-ken 319-11
JAPAN

George B. Hutchinson, M.D., M.P.H.
Department of Epidemiology
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115

Mr. Toshinori Iijima
Division of Reactor Safety Evaluation
Reactor Safety Research Center
Japan Atomic Energy Research Institute
Tokai Research Establishment
Tokai-mura
Naka-gun
Ibaraki-ken 319-11
JAPAN

Dr. Hanspeter Isaak
Section for Accident Consequences
and Emergency Planning
Division of Health Protection
Swiss Nuclear Safety Department
CH-5303 Wurenlingen
SWITZERLAND

Seymour Jablon
National Research Council
National Academy of Sciences
2101 Constitution Avenue
Washington, DC 20418

Dr. Kenneth L. Jackson, Chairman,
Radiological Sciences (SB-75)
University of Washington
Seattle, WA 98185

Prof. Dr. W. Jacobi
Institut Fuer Strahlenschultz
GSF MBH
Ingolstaedter Landstr. 1
D-8042 Neuherberg
FEDERAL REPUBLIC OF GERMANY

H. R. Jammet
Director of Protection
French Atomic Energy
Fontenay - Aux - Roses
92 Houts Du Seine
Paris
FRANCE

David E. Janes
Director, Analysis and Support
Division (ANR-461)
Office of Radiation Programs
US EPA
Washington, DC 20460

Robert Jaske (10)
FEMA
Donohoe Bldg.
Washington, DC 20472

Troyce D. Jones, Ph.D.
Health & Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830

Geoffrey D. Kaiser
Consulting Division
NUS Corporation
910 Clopper Road
Gaithersburg, MD 20878

Dean C. Kaul
Science Applications, Inc.
1701 East Woodfield Road
Suite 819
Schaumburg, IL 60195

Mr. Paul Kayser
Division de la Radioprotection
1, Avenue des Archiducs
LUXEMBOURG

G. Neale Kelly
NII
HSE
Silkhouse Court
Tithebarn Street
Liverpool L2 2LZ
UNITED KINGDOM

George D. Kerr
Health and Safety Laboratory
Oak Ridge National Laboratory
P.O. Box X
Oak Ridge, TN 37830

Matthew Kinnard
Veterans Administration
810 Vermont Avenue, N.W.,
Room 644E
Washington, DC 20502

Peter T. Kirchner, M.D.
Professor of Radiology
Director, Division of
Nuclear Medicine
The University of Iowa
Iowa City, Iowa 52242

J. R. Knight
Oak Ridge National Laboratory
Bulding 6025
P.O. Box X
Oak Ridge, TN 37830

L. Koblinger
Central Research Institute
for Physics
P.O. Box 49
H - 1525 Budapest
HUNGARY

David G. Kocher
Health and Safety Research Division
Oak Ridge National Laboratory
P. O. Box X
Oak Ridge, TN 37831

Dr. John Kollas
Greek Atomic Energy Commission
Aghia Paraskevi
153 10 Attiki
GREECE

Yoshikazu Kumamoto
c/o Dr. Takashi Maruyama
National Institute of
Radiobiological Sciences
9-1, Anagawa 4 chome
Chiba-shi 260
JAPAN

Nan M. Laird, Ph.D.
Department of Biostatistics
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115

Janice Lamb
Building 460
Brookhaven National Laboratory
Upton, NY 11973

Charles E. Land
Radiation Epidemiology Branch
National Cancer Institute
Landow Building, Room 3A22
Bethesda, MD 20205

John Laughlin
Department of Medical Physics
Memorial Hospital
1275 New York Avenue
New York, NY 10021

Mr. Robert Leclere
Servide de Protection contre les
Radiations Ionisantes
Ministere de la Sante publique
et de la Famille
Cite Administrative de l'Etat
Quartier Vesale
B-1000 Bruxelles
BELGIUM

Sheldon G. Levin
Defense Nuclear Agency
Armed Forces Radiobiology
Research Institute
Bethesda, MD 20014

James Liverman
Litton Bionetics, Inc.
5516 Nicholsen Lane
Kensington, MD 20795

William Loewe
Lawrence Livermore National
Laboratory
P.O. Box 808
Livermore, CA 94550

Wayne Lowder
Environmental Measurements
Laboratory
376 Hudson Street
New York, NY 10014

Clarence C. Lushbaugh, M.D.
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, TN 37831

Felix Luykx
Health and Safety Directorate
CEC Batiment Jean Monet (C4-122)
Boite Postale 1907
L-2920 Luxembourg
Grand-Duchy of Luxembourg

John Malik
Mail Stop 670
P.O. Box 1663
Los Alamos National Laboratory
Los Alamos, NM 87545

Daniel Manesse
Institut de Protection et de
Surete Nucleaire (IPSN)
Commissariat a l'Energie Atomique
Centre de'Etudes Nucleaires de
Fontenay-aux-Roses
Boite Postale 6
F-92260 Fontenay-aux-Roses
FRANCE

Eliot Marshall
Science
American Association for the
Advancement of Science
1515 Massachusetts Avenue, N. W.
Washington, DC 20005

T. Maruyama
National Institute of
Radiobiological Sciences
9-1, Anagawa 4 chome
Chiba-shi 260
JAPAN

John M. Matuszek
Department of Health
Empire State Plaza
Albany, NY 12201

Harry Maxon, M.D. (2)
Eugene L. Saenger Radioisotope Laboratory
Mail Location 577
University of Cincinnati
Cincinnati, OH 45267

Roger O. McClellan
Lovelace Inhalation Toxicology
Research Institute
P.O. Box 5890
Albuquerque, NM 87185

Dr. Charles B. Meinhold (3)
Safety and Environmental
Protection Division
Brookhaven National Laboratory
Upton, NY 11973

Edgar Mendelsohn
University of California
Lawrence Livermore National
Laboratory
P.O. Box 808
Livermore, CA 94550

Mortimer L. Mendelsohn
L-452, University of California
Lawrence Livermore National Laboratory
P.O. Box 5507
Livermore, CA 94550

William Mimms
TVA
W10 D179 C-k
400 W. Summit Hill Drive
Knoxville, TN 37902

Dade W. Moeller, Ph.D. (25)
Associate Dean for Continuing Education
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115

R. H. Mole
MRC
Radiobiology Unit
Harwell, OXON
UNITED KINGDOM

Karl Z. Morgan
Department of Physics and Astronomy
Appalachian State University
Boone, NC 28607

Shan Nair
Research Division
Central Electricity Generating Board
Berkeley Nuclear Laboratories
Berkeley
Gloucestershire GL13 9PB
UNITED KINGDOM

Neal Nelson (6)
ANR-460
Office of Radiation Programs
USEPA
Washington, DC 20460

Dr. Jean-Claude Nenot
Departement de Protection (DPr)
Institut de Protection et de
Surete Nucleaire (IPSN)
Commissariat a l'Energie Atomique
Centre d'Etudes Nucleaires de
Fontenay-aux-Roses
Boite Postale 6
F-92260 Fontenay-aux-Roses
FRANCE

W. Roger Ney
National Council on Radiation
Protection and Measurements
7910 Woodmont Avenue, Suite 1016
Bethesda, MD 20814

Leslie Nieves
111 W. Lincoln Ave
Wheaton, IL 60187

William Nixon
United Kingdom Atomic Energy Authority
Safety & Reliability Directorate
Wigshaw Lane
Culcheth
Warrington WA3 4NE
UNITED KINGDOM

K. Nowicki
ORIDI-IO
Institute for Nuclear Research
05-400 Ostock-Swierk
Poland

Oddvar F. Nygaard, Director
Division of Radiation Biology
Department of Radiology
Case Western Reserve University
2058 Abington Road
Cleveland, OH 44106

Prof. Dr. Dr. E. Oberhausen
Abteilung fuer Nuklearmedizin
Der Radiologischen Klinik
Universitaetsklinien
D-6650 Homburg (SAAR)
FEDERAL REPUBLIC OF GERMANY

Keran O'Brien
Environmental Measurements
Laboratory
Radiation Physics Division
376 Hudson Street
New York, NY 10014

Edward P. Radford, M.D.
Radiation Effects Research Foundation
5-2 Hijiyama Park, Minami Ward
Hiroshima 730
JAPAN

M. L. Randolph
Biology Division
Oak Ridge National Laboratory
P.O. Box X
Oak Ridge, TN 37830

Mr. Alfred Renard
Leader, Safety studies
Belgonucleaire S.A.
Rue du Champ de Mars, 25
B-1050 Bruxelles
BELGIUM

H. A. Robitaille
Nuclear Effects Section of the
Protective Sciences Division
R & D Branch
Defence Research Establishment
Ottawa, Ontario K1A OZ4
CANADA

Prof. Dr. Dr. H.R. Roedler
Bundesgesundheitsamt
Institut Fuer Strahlenhygiene
Ingolstaedter Landstr. 1
D-8042 Neuherberg
FEDERAL REPUBLIC OF GERMANY

W. C. Roesch
Pacific Northwest Laboratory
P.O. Box 999
Richland, WA 99352

Harald H. Rossi
Radiological Research Laboratory
Columbia University
630 West 168th Street
New York, NY 10032

Gene E. Runkle (3)
USDOE/AL
ESHD
P. O. Box 5400
Albuquerque, NM 87115

William L. Russell
ORNL
Biology Division
P.O. Box X
Oak Ridge, TN 37830

Eugene L. Saenger, M.D.
Professor of Radiology
University of Cincinnati
College of Medicine
Cincinnati, OH 45267

Leonard A. Sagan
EPRI
P.O. Box 10412
Palo Alto, CA 94303

William J. Schull, Ph.D. (2)
Health Science Center
Graduate School Biomedical Sciences
University of Texas
P. O. Box 20334
Houston, TX 7702

Dr. G. Schwarz
Lotharstrasse 18
D-5100 Aachen
FEDERAL REPUBLIC OF GERMANY

Bobby R. Scott, Ph.D. (2)
Lovelace Inhalation Toxicology
Research Institute
Box 5890
Albuquerque, NM 87185

Steven C. Sholly
UCS
1346 Connecticut Ave. NW
Suite 1101
Washington, DC 20036

Roy E. Shore, Ph.D.
Laboratory of Biostatistics
and Epidemiology
Institute of Environmental Medicine
New York University Medical Center
341 East 25th Street
New York, NY 10010

Warren K. Sinclair, Ph.D.
National Council on Radiation Protection
and Measurements
7910 Woodmont Avenue
Suite 1016
Washington, DC 20014

Jaak Sinnaeve
Radiation Protection Program CEC
Rue de la Loi, 200
B-1049 Bruxelles
BELGIUM

H. Smith
NRPB
Chilton, Didcot
OXON OX11 ORQ
UNITED KINGDOM

H. H. Smith
Biology Department
Brookhaven National Laboratory
Upton, NY 11973

James J. Smith
Veterans Administration
810 Vermont Avenue, N.W.,
Room 644E
Washington, DC 20502

Gerald A. Soffen
Division of Life Sciences (SB-3)
National Aeronautics and Space
Administration Headquarters
Washington, DC 20546

Juan Bagues Somonte
Junta de Energia Nuclear
Ciudad Universitaria
Avenida Complutense, 22
Madrid-3
SPAIN

Lewis V. Spencer
National Bureau of Standards
Washington, DC 20234

Eli Stern
Israel Atomic Energy Commission
P. O. Box 7061
Tel Aviv 61070
ISRAEL

T. Straume
University of California
Lawrence Livermore National Laboratory
P.O. Box 808
Livermore, CA 94550

Prof. Dr. C. Streffer
Institut Fuer Med. Strahlenphysik
Universitaetsklinikum
Hufelandstr. 55
D-4300 Essen
FEDERAL REPUBLIC OF GERMANY

Carl Stroud
Defense Nuclear Agency
Washington, DC 20305

Paul Strudler
National Institute for Occupational
Safety and Health, Center for
Disease Control
Parklawn Building, Room 848
Rockville, MD 20857

Charles D. Stutzman
Cancer Branch
Chronic Diseases Division, CEH
Center for Disease Control
Atlanta, GA 30333

Jacob W. Thiessen
Office of Energy Research
ER-71, GTN
USDOE
Washington, DC 20545

Stephen R. Thomas, Ph.D. (2)
Radiology Department
E456 Medical Science Building
University of Cincinnati Medical Center
Mail Location #579
Cincinnati, OH 45267-0579

Soren Thykier-Nielsen
Health Physics Department
Riso National Laboratory
Postbox 49
DK-4000 Roskilde
DENMARK

Prof. G. I. Tract, A.A., O.B.E.
2403 Georgene Dr. NE
Albuquerque, NM 87112

Prof. Dr. K. R. Trott
Institute Fuer Biologie
GSF MBH
Ingolstaedter Landstr. 1
D-8042 Neuherberg
FEDERAL REPUBLIC OF GERMANY

Ulf Tveten
Institute for Energy Technology
Postboks 40
N-2007 Kjeller, NORWAY

Carl Uhruh
P.O. Box 999
Battelle Northwest Laboratories
Richland, WA 99352

Arthur C. Upton
Professor and Chairman
Department of Environmental Medicine
New York University Medical Center
550 First Avenue
New York, NY 10016

Carlos Corres Vidal
Departmento De Tecnologia Nuclear
E.T.S. Ingenieros Industriales
Universidad Politecnica
De Madrid
SPAIN

John Villforth (3)
Director of Center for
Devices and Radiological Health
Food and Drug Administration
5600 Fischers Lane
Rockville, MD 20857

Prof. Dr. F. Vogel
Institut Fuer Anthropologie
UND Humangenetik
Universitaet Heidelberg
IM Neuenheimer Feld 328
D-6900 Heidelberg
FEDERAL REPUBLIC OF GERMANY

Frank Von Hipple
Center for Environmental Studies
Princeton University
Princeton, NJ 08544

Seppo Vuori
Technical Research Centre of Finland
Nuclear Engineering Laboratory
P. O. Box 169
SF-00181 Helsinki 18
FINLAND

Neil Wald, M.D.
Universsity of Pittsburgh Graduate
School of Public Health
RC-510 Scaife Hall
Pittsburgh, PA 15261

Ian B. Wall
EPRI
3412 Hillview Ave.
P. O. Box 10412
Palo Alto, CA 94303

I. L. Wang
Taiwan Power Co.
242 Roosevelt Road
Sec. 3
Taipei, Taiwan
REPUBLIC OF CHINA

Geoffrey A. M. Webb
National Radiological Protection
Board
Chilton, Didcot
Oxfordshire
OX11 ORQ
ENGLAND

Edward W. Webster, Ph.D.
Diagnostic Radiology
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

D. Weiss
National Academy of Sciences
National Research Council
2101 Constitution Avenue
Washington, DC 20418

Paul P. Whalen
Mail Stop 625
P.O. Box 1663
Los Alamos National Laboratories
Los Alamos, NM 87545

Frank Williamson
Biology Division
Argone National Laboratory
Argonne, IL 60439

Raymond A. Winyard
NII
Thames House North
Millbank
London SWIP 4QJ
UNITED KINGDOM

Rodney Wong
Environmental Epidemiological
Branch
Landow Building, Room 3C07
National Cancer Institute
Bethesda, MD 20205

Keith Woodard
Pickard, Lowe & Garrick, Inc.
1200 18th Street, N.W.
Suite 612
Washington, DC 20036

Steven W. Woolfolk
ARA, Inc.
4300 San Mateo Blvd. NE
Albuquerque, NM 87110

Harold O. Wyckoff
National Council on Radiation Protection
and Measurements
7910 Woodmont Avenue, Suite 1016
Washington, DC 20014

Rosalyn S. Yalow
Senior Medical Investigator
Veterans Administration Medical Center
130 West Kingsbridge Road
Bronx, NY 10468

R. Young
Armed Forces Radiobiology
Research Institute
Bethesda, MD 20014

Victor H. Zeve
Special Assistant
Office of the Director
National Cancer Institute
Building 31, Room 4B47
Bethesda, MD 20205

Zhang Ben-Zheng
Institute of Nuclear Energy Technology
Qing-Hua University
P. O. Box 1021
Beijing
PEOPLE'S REPUBLIC OF CHINA

2564 G. W. Smith
3141 C. M. Ostrander (5)
3151 W. L. Garner
6321 R. E. Luna
6321 R. M. Ostmeyer
6400 A. W. Snyder
6410 J. W. Hickman
6411 A. S. Benjamin
6412 A. L. Camp
6414 D. M. Ericson
6415 D. J. Alpert (25)
6415 D. I. Chanin
6415 J. M. Griesmeyer
6415 F. E. Haskin
6415 J. C. Helton
6415 L. T. Ritchie
6415 J. L. Sprung
6417 D. D. Carlson
6420 J. V. Walker
6431 R. M. Cranwell
6440 D. A. Dahlgren
8024 M. A. Pound

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John S. Evans, Dade W. Moeller, Douglas W. Cooper
Sandia Project Officer: Daniel J. Alpert

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Analysis of the radiological health effects of nuclear power plant accidents requires models for predicting early health effects, cancers and benign thyroid nodules, and genetic effects. Since the publication of the Reactor Safety Study, additional information on radiological health effects has become available. This report summarizes the effort of a program designed to provide revised health effects models for nuclear power plant accident consequence modelling. The new models for early effects address four causes of mortality and nine categories of morbidity. The models for early effects are based upon two parameter Weibell functions. They permit evaluation of the influence of dose protraction and address the issues of variation in radiosensitivity among the population. The piecewise-linear dose-response models used in the Reactor Safety Study to predict cancers and thyroid nodules have been replaced by linear and linear-quadratic models. The new models reflect the most recently reported results of the follow-up of the survivors of the bombings at Hiroshima and Nagasaki and permit analysis of both morbidity and mortality. The new models for genetic effects allow prediction of genetic risks in each of the first five generations after an accident and include information on the relative severity of various classes of genetic effects. The uncertainty in modelling radiological health risks is addressed by providing central, upper and lower estimates of risks. An approach is outlined for summarizing the health consequences of nuclear power plant accidents.

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