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Health Effects Models for Nuclear Power Plant Accident Consequence Analysis

Low LET Radiation

Part II: Scientific Bases for Health Effects Models

Prepared by S. Abrahamson, M. Bender, S. Book, C. Buncher, C. Denniston, E. Gilbert, F. Hahn, V. Hertzberg, H. Maxon, B. Scott, W. Schull, S. Thomas

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Under Contract to:
Sandia National Laboratories
Albuquerque, NM 87185

S. Yaniv, NRC Project Manager

Division of Regulatory Applications
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, DC 20555
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ABSTRACT

This report provides dose-response models intended to be used in estimating the radiological health effects of nuclear power plant accidents. Models of early and continuing effects, cancers and thyroid nodules, and genetic effects are provided.

Two-parameter Weibull hazard functions are recommended for estimating the risks of early and continuing health effects. Three potentially lethal early effects--the hematopoietic, pulmonary and gastrointestinal syndromes—are considered. In addition, models are provided for assessing the risks of several non-lethal early and continuing effects—including prodromal vomiting and diarrhea, hypothyroidism and radiation thyroiditis, skin burns, reproductive effects, and spontaneous abortions.

Linear and linear-quadratic models are recommended for estimating cancer risks. Parameters are given for analyzing the risks of seven types of cancer in adults—leukemia, bone, lung, breast, gastrointestinal, thyroid and "other". The category, "other" cancers, is intended to reflect the combined risks of multiple myeloma, lymphoma, and cancers of the bladder, kidney, brain, ovary, uterus and cervix. Models of childhood cancers due to in utero exposure are also provided. For most cancers, both incidence and mortality are addressed. The models of cancer risk are derived largely from information summarized in BEIR III—with some adjustment to reflect more recent studies. The effect of the revised dosimetry in Hiroshima and Nagasaki has not been considered.

Linear and linear-quadratic models are also recommended for assessing genetic risks. Five classes of genetic disease—dominant, x-linked, aneuploidy, unbalanced translocations and multifactorial diseases—are considered. In addition, the impact of radiation-induced genetic damage on the incidence of peri-implantation embryo losses is discussed.

The uncertainty in modeling radiological health risks is addressed by providing central, upper, and lower estimates of all model parameters. Data are provided which should enable analysts to consider the timing and severity of each type of health risk.

ACKNOWLEDGEMENTS

This report reflects the efforts of many individuals. Primary among these are the Working Group leaders—Dr. Bobby Scott, Lovelace Inhalation Toxicology Institute; Dr. Ethel Gilbert, Battelle Pacific Northwest Laboratories; Dr. Seymour Abrahamson, University of Wisconsin; and Dr. Harry Maxon, University of Cincinnati—who were responsible for reviewing the literature, making recommendations for dose-response models, and preparing reports summarizing their findings. Drs. Douglas Cooper and Dade Moeller of Harvard University—who coordinated the selection of the Working and Advisory Groups and were instrumental in initiating the project—also deserve special mention.

The entire effort has benefitted immeasurably from the efforts of the members of Advisory Committee:

Seymour Abrahamson, Ph.D	University of Wisconsin
William J. Bair, Ph.D	Battelle Pacific Northwest Laboratories
Michael A. Bender, Ph.D	Brookhaven National Laboratory
Bruce B. Boecker, Ph.D	Lovelace Inhalation Toxicology Research Institute
Victor P. Bond, M.D., Ph.D	Brookhaven National Laboratory
Richard G. 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
Marvin Goldman, Ph.D	University of California
George B. Hutchison, 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

The members of the Advisory Committee critically reviewed both the original report and this revision of that report. Every effort has been made to respond to their comments. Nevertheless membership on the Advisory Committee should not be taken to imply either individual or collective endorsement of the health effects models.

Many other scientists have made significant contributions to the development of the models presented in this report. Drs. Niel Wald, Albert Spritzer, and Joseph Watson of the University of Pittsburgh

reviewed data on human radiation injury that was used in the development of the early health effect models. Drs. Roy Shore and Nan Laird provided technical information that supported development of the skin and thyroid cancer models. Chapter reviews were provided by the following experts: Drs. Gilbert Beebe and Charles Land, National Cancer Institute; Dr. Thomas Cochran, National Resources Defense Council; Dr. James Crow, University of Wisconsin; Drs. Troyce Jones and Clarence Lushbaugh, Oak Ridge National Laboratory; and Dr. Robert Young, Defense Nuclear Agency.

CONTENTS

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Concluded)

FIGURES

FIGURES (Concluded)

TABLES

TABLES (Continued)

TABLES (Continued)

TABLES (Continued)

TABLES (Concluded)

1.0 INTRODUCTION

For several decades there has been interest in predicting the health effects of 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 (NRC, 1975). The health effects models developed for the Reactor Safety Study have provided the basis for most of the official estimates of the health consequences of nuclear power plant accidents. They are used in several health consequence computer codes, e.g., CRAC.

In 1981 the NRC, through a contract with Sandia National Laboratories, began a critical review of the Reactor Safety Study health effects models. The review, which was directed by Dr. Douglas W. Cooper at Harvard University, concluded that several components of the Reactor Safety Study health effects models required revision.

In the Fall of 1982 the NRC initiated an effort to prepare improved health effects models to replace those used in the Reactor Safety Study. An Advisory Group, consisting of fifteen experts, was assembled. Nominations for appointment to the Advisory Group were solicited from over three hundred scientists. The Advisory Group was responsible for oversight and review of the model development process and for assisting in the selection of Working Groups.

The Working Groups were responsible for conducting literature reviews, making recommendations for health effects models, and preparing reports giving the scientific basis for each model recommended. The entire project was managed by a group of scientists at Harvard University, led initially by Dr. Douglas W. Cooper and later by Dr. John S. Evans.

The first draft of NUREG-CR/4214 was completed in the Summer of 1983. It was reviewed at a meeting of the Working Group Chairpersons on 29 August 1983 and, after minor revisions, at a joint meeting of the Advisory and Working Groups on 26-27 January 1984. A second draft of the report was completed in the Summer of 1984. It was reviewed by the Advisory Group, the Working Groups, Sandia National Laboratories, the NRC, and a small group of external reviewers who had not been involved in the model development process.

NUREG-CR/4214 was published in July of 1985. The NRC circulated the document widely. More than 1000 copies of the report were distributed for public review and comment. Formal public presentations of the new models were made in Washington, DC on 10 October 1985, and in Luxembourg on 19 April 1985.

In the Spring of 1987, the NRC initiated a project to further revise the models. One of the primary goals of the revision was to ensure that the models for early effects were consistent with data on humans who had been

accidentally or therapeutically exposed to radiation. A group of scientists at the University of Pittsburgh, led by Dr. Niel Wald, was retained to review the available human data; to assist in the interpretation of that data; and to recommend values of population injury thresholds based on the human data. A second goal was to develop upper and lower estimates of parameters for all early effects to reflect the uncertainties inherent in the models. Drs. Bobby Scott and Fletcher Hahn of the Lovelace Inhalation Toxicology Research Institute, the developers of the early effects models presented in the original report, were retained to revise those models. The NRC was particularly concerned that the original parameters for pulmonary syndrome mortality be critically reviewed.

In addition to achieving these two primary goals, the NRC sought to update the models for late somatic effects to reflect the continuing followup of the survivors of the atomic bombings at Hiroshima and Nagasaki and to expand the definition of genetic effects to include consideration of the peri-implantation embryo losses induced by radiation. The authors of the late somatic effects and genetic effects chapters of the original report, Dr. Ethyl Gilbert and Dr. Seymour Abrahamson, were asked to review their chapters in response to these concerns.

The revisions to the late somatic effects and genetic effects chapters were relatively minor and were completed by the end of the Summer of 1987. The revisions of the early effects models were much more extensive and were completed in two phases. The first phase reviewed the human data on early effects and developed lower, central, and upper estimates of parameter values for all of the early effect models. The revised parameter values were selected in a series of meetings of the early effects working group. In the course of these meetings, the working group determined that models which explicitly accounted for the dependence of risk on dose rate would be desirable. The second phase developed such models for bone marrow and pulmonary syndrome mortality. The revised early effects models including the new dose rate models were completed in the Fall of 1988.

This report, which has been published in two volumes, represents an effort to summarize the revised models, to describe the sources of recommended model parameters, and to discuss the bases for key assumptions. Part I: Introduction, Integration and Summary, which was prepared by the group at Harvard charged with oversight of the project, is an overview intended to make the models available to the widest possible audience. It assumes only rudimentary familiarity with mathematics and little prior knowledge of biology or health physics. Part II: Scientific Bases for Health Effects Models, which was prepared by the scientists in the various working groups, is intended to provide epidemiologists, radiobiologists and other health scientists with detailed information on the origins of the models.

The models presented in this report are intended for use in nuclear power plant accident consequence analysis. They represent one element of a much larger effort to improve the computer codes used by the NRC to estimate the health and economic consequences of various potential accident scenarios. Other components of the accident consequence codes consider the probabilities of initiating events, the likelihood and magnitude of the releases, the environmental fate and transport of radionuclides, and the organ-specific doses expected. Although important, these topics are not addressed in this report. Interested readers should consult, for example, the PRA Procedures Guide (USNRC, 1983) for discussions of these matters.

The report is not intended as a guide for physicians or others involved in the handling of radiation emergencies. It is also not intended to represent a compendium of information on radiobiology. Its purpose is simply to document the dose-response models recommended for estimating the health effects of nuclear power plant accidents.

1.1 Treatment of Uncertainty

The health risks caused by radiation cannot be predicted precisely. The initial statement of work leading to this report (Sandia, 1983) reflected an awareness of this and sought:

> . . . a realistic 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.

The uncertainties in modeling health risks are of two types—parameter uncertainties and model uncertainties. Parameter uncertainty arises in the process of drawing inferences about processes which are to some extent random (or are observed with error) from small samples. If this were the only source of uncertainty, it would be relatively simple to provide complete descriptions of the uncertainty in each of our estimates of health risk. Unfortunately, the other source of uncertainty—model uncertainty—is not amenable to simple analysis. Model uncertainty arises from the need to rely on analogy. For example, estimates of the risks of pulmonary syndrome mortality are based in part on evidence from studies of beagles. The accuracy of such estimates depends on the adequacy of the analogy. Similarly, most estimates of radiation-induced cancer risk are based on studies of the survivors of the bombings at Hiroshima and Nagasaki. Again, the accuracy of the extrapolation from the high doses and high dose rates received by the Japanese survivors to the low doses and dose rates frequently of interest depends on the validity of the analogy. Estimation of the extent of the uncertainty in these analogies is unavoidably subjective.

We have taken a first step toward addressing uncertainty by providing three estimates of each effect—a central estimate, a lower estimate and an upper estimate. The central estimates are intended to be realistic estimates—reflecting the judgment of the scientists involved in model development. The upper and lower estimates are intended to reflect alternative assumptions that are reasonably consistent with available evidence and that may be preferred by some scientists.

The uncertainties in estimating the health effects induced by exposure to radiation are considerable. In view of this, it is important that accident consequence analyses consider the spectrum of possible consequence estimates rather than focusing attention on the central estimates.

2.0 EARLY OCCURRING AND CONTINUING EFFECTS

B. R. Scott and F. F. Hahn
Lovelace Inhalation Toxicology Research Institute

Executive Summary

This chapter develops health-risk models for early and continuing effects of exposure to beta or gamma radiation that could be associated with light water nuclear power plant accidents. The main purpose of the chapter is to provide details on each health-risk model and on the data used. Early and continuing effects considered are prodromal symptoms and nonneoplastic diseases that usually occur soon after a brief radiation exposure. These effects are generally associated with relatively high (greater than 1 Gy) absorbed organ doses. For most of the effects considered, there is an absorbed organ dose threshold below which no effects are seen.

Some information is provided on health effects observed in victims of the Chernobyl power plant accident. However, the information is not intended to imply that a similar accident scenario is considered possible in the U.S. There are major differences between the RBMK-type reactor used in the U.S.S.R and the power reactors used in the U.S.

Throughout the chapter, the absorbed dose D refers to the absorbed organ dose, total body dose, or midline tissue dose. The phrase "brief exposure" is used to indicate short to intermediate exposure times ranging from less than a minute (e.g., prompt) to about 2 days. The phrase "protracted exposure" refers to more prolonged exposure times (e.g., over weeks or months).

Organs of primary interest, because of their high sensitivity or their potential for receiving large doses, are bone marrow, gastrointestinal tract, thyroid glands, lungs, skin, gonads, and eyes. Exposure of the fetus is also considered. Additional data and modeling techniques available since publication of the Reactor Safety Study were used to obtain models for morbidity and mortality.

Major morbidity effects modeled in this chapter are (1) diarrhea, (2) prodromal vomiting, (3) permanent ovulation suppression in females, (4) temporary sperm count suppression in males, (5) radiation thyroiditis, (6) hypothyroidism, (7) skin erythema, (8) transepithelial injury of the skin, (9) mental retardation after irradiation *in utero*, (10) growth retardation (small head size) after irradiation *in utero*, and (11) cataracts. Available information was not sufficient to model permanent sperm count suppression in males or temporary suppression of ovulation in females.

As in the Reactor Safety Study, three possible modes of death are modeled: (1) death associated with injury to the bone marrow, (2) death

associated with injury to the gastrointestinal tract, and (3) death associated with injury to the lungs.

The reduction in lethality risks due to medical intervention is also considered. Three categories of medical treatment are discussed: minimal, supportive, and intensive (called "heroic" in the Reactor Safety Study). Minimal treatment involves basic first aid in a clean environment. Supportive treatment includes hospitalization with routine isolation procedures (i.e., not including laminar airflow), electrolyte replacement, administration of blood products (especially fresh platelets), treatment with broad-spectrum antibiotics and parenteral feeding. Intensive treatment includes, in addition to supportive treatment, extraordinary procedures such as bone marrow transplantation and the use of colony stimulating factors. The categories of medical treatment discussed in this chapter should not be regarded as instructions to physicians but rather as guides for estimating the number of deaths following an accident at a light water nuclear power plant.

Lethality dose-response models are provided for only two categories of medical treatment (minimal, supportive). Because of the limited range of dose (6 to 9 Gy) over which intensive treatment is thought to be useful, and the limited number of persons likely to receive radiation doses to bone marrow in this range, we do not expect off-site health effects calculations to be significantly affected by individuals in this treatment category. No model is provided for estimating mortality risk for individuals given intensive treatment.

A number of different types of risk estimators were used in the Reactor Safety Study to model early and continuing effects. Upon review, it was concluded that most of the effects could be described using the same type of risk estimator (Weibull-type). While the Weibull is only one of a number of functions that provide sigmoid-type dose-response curves, it has the distinct advantage in the ease with which it can be applied, particularly with computer software. Therefore, most of the revised models are based on the Weibull dose-response function. The exception is hypothyroidism, for which a linear-threshold model is used to be consistent with the model currently used by the NRC.

The Weibull-type function used to estimate risk depends on two parameters: (1) the dose D_{50}, which is the dose expected to affect 50 percent of those exposed, and (2) the shape parameter V, which determines the shape of the dose-effect relationship. For lethal effects, D_{50} represents the lethal dose to 50 percent of the population (LD_{50}), while for morbidity effects, it represents the effective dose to 50 percent of the population (ED_{50}). Data for incidence versus dose were used to obtain estimates of model parameters. Estimates of the D_{50} were obtained for each effect of interest except hypothyroidism.

To account for dose rate effects, a hazard-function modeling approach was used to estimate the risk of lethality from a specific cause (e.g., bone

marrow dysfunction), or the risk of a specific morbidity (e.g., prodromal vomiting). With the hazard-function approach, one finds the lethality or morbidity cumulative hazard H as a function of the normalized dose X, in units of LD_{50} (for lethality) or ED_{50} (for morbidity). With this unit of dose, X = 1 would correspond to an LD_{50} when lethality is the endpoint modeled. A dose X = 0.5 would correspond to one-half of the LD_{50}. Similar definitions apply to morbidity. The risk of the effect of interest is related to the lethality or morbidity hazard H by the expression:

$$\text{Risk} = 1 - \exp[-H].$$

For brief exposure at a fixed dose rate, the normalized dose X for lethality from a specific cause is simply the cumulative absorbed dose D to the organ of interest (e.g., bone marrow) divided by the LD_{50} appropriate for the fixed dose rate. For protracted (low dose rate) exposure at a fixed dose rate, X is evaluated in the same way, with an LD_{50} appropriate for the low dose rate exposure. With this approach, LD_{50} as a function of dose rate is used to normalize different absorbed radiation doses D delivered at different dose rates. For variable dose rates, different parts of the dose are divided by different LD_{50}s to account for effects of a changing dose rate. The same approach is used in estimating the risk of a specific morbidity, with ED_{50}s being used instead of LD_{50}s in the normalizations.

For brief exposure at a high dose rate, followed by protracted exposure at a low dose rate, the normalized doses for the brief and protracted exposures are added to obtain the total dose X.

A judgmental cutoff dose rate of 0.06 Gy/hr (0.1 rad/min) was selected to distinguish between brief high dose rate and protracted low dose rate exposures. Dose rates greater than or equal to 0.06 Gy/hr were considered brief high rates; dose rates less than 0.06 Gy/hr were considered protracted low rates.

The ED_{50}s for cataracts, permanent suppression of ovulation in females, 2-year sperm count suppression in males, severe mental retardation, fetal death, and for small head size after exposure in utero, were estimated only for the brief high dose rate category because of limited data or because doses required to produce the effect would be lethal. For radiation thyroiditis, the ED_{50} was estimated only for the protracted low dose rate category because of limited data.

Risk functions for most early and continuing effects are of the threshold-type; therefore, a given dose may be at or below the threshold. If so, the risk for that dose is then estimated to be zero. For acute lethality from injury to the bone marrow, one-half of a median lethal dose is the central estimate of the threshold. Thus, if X is less than or equal to 0.5, the hazard function H is calculated to be zero which leads to a risk estimate of zero. Incorporation of the threshold dose in this manner can cause a discontinuity in the dose-effect relationships at

the threshold dose, but this has little impact on the aggregate estimated deaths and morbidities predicted by the model for a nuclear reactor accident.

Two general categories for exposure are considered: (1) brief, high dose rate exposure mainly to external gamma rays from a passing radioactive cloud (cloud shine) and from the radionuclide-contaminated ground surface (ground shine) followed by (2) protracted, low dose rate internal exposure to beta and gamma radiations emitted by inhaled and ingested radionuclides. Alpha radiation was assumed to contribute only a small fraction of the dose, and was not considered in any of the models developed.

For acute lethality, injuries to the bone marrow, intestines, and lung are considered most important. Because a lethal dose to the central nervous system would also be accompanied by lethal doses to these organs, a risk function specifically for lethality from injury to the central nervous system is unnecessary. Lethal injury from radiation skin burns is not considered a significant risk for nuclear power plants in the U.S. No model is provided for this mode of lethality.

The hazard-function method used to model the effect of brief high dose rate followed by protracted low dose rate irradiation is based on the cumulative hazard H. Different types of mathematical functions could have been used to represent H. We have used the following Weibull-type cumulative hazard function because of its versatility and usefulness in modeling dose rate effects:

$$H = \ln(2)X^{V} \quad .$$

The parameter V is called the shape parameter because it determines the shape of the dose-response curve. One first arrives at an estimate of the cumulative hazard H; the risk can then be arrived at indirectly.

An advantage of using the Weibull model and hazard-function approach is in the treatment of dose rate effects. Another advantage is in modeling early and continuing effects of combined exposure to high- and low-LET radiations. For example, if X_L and X_H are the total organ-specific low- and high-LET normalized doses to a given organ, then the total dose X for that organ is the sum of these doses.

To calculate the total lethality risk from all early and continuing effects considered, the cumulative hazards for each lethal mode of injury considered (bone marrow, intestines, and lung) are added to arrive at an overall lethality hazard. The central estimate of risk of lethality from these three competing modes is:

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

where

$$H_{early} = H_{bone} + H_{gastrointestinal} + H_{lung} \quad .$$

When reliable data from exposures of humans were available, they were used to estimate the shape parameter V and/or D_{50} for morbidity or mortality effects. When such data were not available or were ambiguous, data from exposures of laboratory animals were used to estimate these parameters.

The many sources of uncertainty that could have an effect on accuracy of the risk estimates include: (1) uncertainty in dose estimates; (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; (7) uncertainty about the distribution of radiosensitivity among the populations at risk; (8) uncertainty in threshold dose; and (9) uncertainty in how to deal with nonuniform exposure.

A complete investigation of these uncertainties is beyond the scope of this chapter. However, to facilitate the evaluation of uncertainty, upper and lower bounds have been provided for model parameters. In some cases, the bounds are judgmental.

The judgmental bounds resulted from a series of meetings of the working group, comprised of the two authors of this chapter along with Dr. John S. Evans (Harvard University), Dr. Jeremy L. Sprung (Sandia National Laboratories), Dr. Shlomo S. Yaniv (Nuclear Regulatory Commission) and three faculty members of the University of Pittsburgh: Dr. Niel Wald, Dr. Joseph A. Watson, and Dr. Albert A. Spritzer. The University of Pittsburgh's team of Drs. Wald, Watson and Spritzer reviewed relevant publications on early and continuing effects of irradiation published after the Reactor Safety Study and not included in the earlier version of this report (NUREG-CR/4214, 1985), and provided valuable data and references for this chapter.

The risk estimators discussed in the chapter were developed mainly for nuclear power plant accident consequence modeling. Taken together, the models should permit adequate analysis of the early health effects of nuclear power plant accidents.

2.1 Introduction

2.1.1 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, and was developed to improve upon estimates used in the Reactor Safety Study (WASH 1400, 1975). Since publication of these studies, additional data and models have become available, and were considered in obtaining the revised health-risk estimates described in this chapter.

The refined health-risk models have parameters that depend on dose rate and include morbidity effects not in the original Reactor Safety Study health effects model. An earlier version of this work is reported elsewhere (Scott and Hahn, 1985).

2.1.2 Approach

2.1.2.1 Sources of Information

Throughout this chapter, data based on radiation exposures of humans are used when applicable human data are available and the uncertainty in the data is relatively small. However, for specific types of exposures where data from human studies 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. A dose-rate-dependent model (Scott et al., 1988a) was used to obtain the median lethal dose for acute lethality from injury to the bone marrow. The model was adapted for acute lethality from irradiation of the lung.

In most cases, information on morbidity was too limited to formulate reliable predictions of dose-rate effects. Also, sensitive subpopulations (for example, the aged, the sick, etc.) are expected to make up a small but significant part of the exposed population at risk, for both mortality and morbidity. Insufficient information is available, except perhaps on effects of irradiation of the lungs in different age groups, to derive reliable risk estimates for specific subpopulations. Uncertainties in risks from radiation exposure can be evaluated by the method of sensitivity analysis using the upper and lower bounds provided for model parameters.

2.1.2.2 Characteristics of Types of Exposures and Effects

Early and continuing effects of irradiation considered in this chapter include the major nonstochastic effects that normally occur within the first year after radiation exposure although some manifestations may continue to appear later. They are generally associated with relatively high radiation doses; their severity is less with smaller radiation dose. This dose-responsive relationship implies that there is usually a dose threshold for early effects below which no effects are seen. Effects characterized by a threshold dose and by a severity that increases with dose are called nonstochastic (ICRP 41, 1984). Threshold doses to a given organ are smaller for morbidity than for lethality. Where appropriate, dose thresholds have been estimated. Upper and lower bounds are also provided.

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 continuous exposure modes are considered in the model. Health risks are considered for effects that occur in individual organs, although the radiation exposure may involve several organs or the total body. Using a specific organ approach facilitates evaluating the combined effects from external irradiation and from internal emitters.

Throughout the chapter, radiation dose refers to the average absorbed dose to the total body, specific organ of interest (e.g., bone marrow), or to the midline tissue. For external radiation, total-body exposure is assumed. Dose rate refers to the average absorbed dose rate to the target of interest over a specified time period.

High radiation doses to the total body from external sources 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 potential for receiving a large radiation dose, are bone marrow, gastrointestinal tract, thyroid gland, lung, skin, gonads, and eyes. The fetus is also of primary interest.

2.1.2.3 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 exposure to several organs. A detailed description of this methodology is provided elsewhere (Scott et al., 1984; Scott et al., 1988a, 1987). The cumulative hazard (H) is related to risk of mortality (morbidity). If the cumulative hazard is known, the risk can be calculated. Cumulative hazards can be defined by a number of different functions. A two-parameter Weibull function is used to describe the dose-effect relationship, because it adequately represents the available data and facilitates development of computer software for predicting the early effects.

2.1.2.3.1 Lethality and Morbidity Hazard

For lethality, the cumulative hazard is called the lethality hazard; for morbidity, it is called the morbidity hazard. The general expression used for the lethality or morbidity hazard is:

$$H = \ln(2)(D/D_{50})^{V} = \ln(2)X^{V} \qquad (1)$$

where D is the radiation dose, D_{50} is that dose which produces the effect of interest in 50 percent of the population at risk, and V is a parameter (shape parameter) which determines the shape of the dose-effect curve.

The ratio D/D_{50} in Equation 1 represents a dimensionless dose (normalized) in units of the D_{50}; we call this dose X, i.e., $X = D/D_{50}$. There are some advantages in using the normalized dose X instead of the dose D in the analysis of data for early effects of irradiation (Scott et al., 1988a, 1987, 1988b; Scott, 1988a, 1987, 1988b; Jones, 1981). Use of X instead of D eliminates much of the variability in dose-response relationships associated with different mammalian species, with differences in linear energy transfer (LET) (Jones, 1981), and with differences in dose rate (Scott et al., 1988a). Details on how to determine the shape parameter V for combined exposure to different radiations (e.g., alpha, beta, and gamma) are provided elsewhere (Scott, 1989; Scott et al., 1989).

2.1.2.3.2 Risk Function

The risk of morbidity or lethality is related to H by the expression:

$$\text{Risk} = 1 - \exp(-H) \quad . \tag{2}$$

The median effective dose (D_{50}) for each effect depends on the dose rate and how it changes over time. To account for effects of variable dose rates, doses delivered in consecutive infinitesimal time intervals can be normalized to account for changes in dose rate over the intervals (Scott et al., 1988a). The normalization leads to use of dose X, expressed in units of D_{50}, as the independent variable, rather than cumulative radiation dose D. A value X = 1 represents a median lethal dose. This method is similar to calculating rem or Sv doses, but allows for a varying RBE. Multiplying X by the D_{50} in rad or Gy for the reference exposure dose rate leads to an equivalent dose in rad or Gy, respectively.

In the ideal case, the normalized dose is evaluated using:

$$X = \int \dot{D} \; D_{50}(\dot{D})^{-1} \; dt \quad ,$$

where the integration is over the time of exposure, for a continuous irradiation pattern; $\dot{D}$ is the instantaneous absorbed dose rate to the organ of interest evaluated at exposure time t, and the normalization function $D_{50}(\dot{D})$ depends on dose rate.

For nuclear accident risk assessment, an exact evaluation of the integral may not be practical, as computer time for a population dose and dose-rate distribution could be sizable. In such cases, the integral can be approximated using one of at least three approaches: (1) the variable-parameter approach where the model parameter D_{50} depends on dose rate and changes for each of n preselected time intervals; (2) the fixed-parameter approach (Scott and Hahn, 1985) where the model parameter D_{50} does not change with dose rate but differs for each of n preselected consecutive

time intervals to account for expected changes in dose-rate patterns over the intervals (e.g., high dose rates initially, followed by intermediate dose rates, followed by low dose rates); or, (3) using a crude fixed-parameter approach where the model parameter D_{50} changes only when the dose rate enters specific wide dose-rate ranges (e.g., brief high dose rates, vs. protracted low dose rates).

With each of the 3 approaches, the solution to the integral for the normalized dose can be approximated by an expression of the form:

$$X \simeq D_1/D_{50,1} + D_2/D_{50,2} + \ldots D_n/D_{50,n} \quad .$$

For the variable-parameter or fixed-parameter consecutive-time-interval approaches, D_1, D_2, . . . , D_n would represent the absorbed radiation doses in the time intervals indicated by the subscripts. The normalization parameters are indicated by $D_{50,1}$, $D_{50,2}$ . . . , $D_{50,n}$, with the subscript again indicating the time period of applicability. With the variable-parameter approach, the normalization parameters will be different for different average dose rates in the same time interval. For the fixed parameter approach, they will remain fixed at values preselected to account for changes in dose rate pattern over the consecutive intervals (Scott et al., 1987).

With the variable-parameter approach, a model is needed for estimating the D_{50} for different average dose rates that arise in the consecutive time intervals. However, because suitable models are currently available only for acute lethality from the hematopoietic or pulmonary modes, the variable-parameter approach can presently be used only for acute lethality from these two modes. For most other acute quantal effects of interest, a crude fixed-parameter model can be used with only two values for the D_{50} being defined: one for brief high-dose rates, and one for protracted low-dose rates. The judgmental cutoff between brief high-dose-rate and protracted low-dose-rate irradiation is 0.06 Gy/hr (0.1 rad/min), and is based on an exploratory analysis of limited data on the influence of dose rate on the D_{50}.

Larger systematic errors are associated with the fixed parameter approach than with the consecutive-time-interval approaches. To compensate for systematic error, bounds are provided for parameters in most of the fixed-parameter models. For results derived from use of the crude fixed-parameter approach, it is recommended that upper and lower bounds be reported on expected cases of morbidity, along with or in the absence of central estimates.

In some instances, no D_{50} parameter is provided for normalization of the protracted dose (e.g., cataracts, sperm count suppression in males, ovulation suppression in females); this is because, for nuclear reactor scenarios, protracted doses large enough to cause the effect (e.g.,

cataracts) would also cause death from injury to the bone marrow, or because of limited data.

Competing modes of death (from bone-marrow injury, gastrointestinal injury, or lung injury) are modeled in a way equivalent to that used in the Reactor Safety Study (WASH 1400, 1975). Lethality hazards H_{bone}, $H_{gastrointestinal}$, and H_{lung} account for lethal effects of injury to these organs. The total lethality hazard for death from one or more of these three early effects is given by H_{early}, which is equal to the sum of the three lethality hazards $H_{bone} + H_{gastrointestinal} + H_{lung}$. The lethality risk is then evaluated using:

$$\text{Risk} = 1 - \exp[-H_{early}] \quad .$$

This hazard-function modeling approach can be extended to include other lethality hazards including one or more terms for interaction effects.

The following examples are provided to clarify the use of the normalized dose X in evaluation of risk for complex patterns of low-LET irradiation. Other publications provide additional examples of its use (Scott et al., 1988a, 1987, 1988b).

Example: Suppose that following a nuclear accident, an individual received 1.85 Gy of external gamma rays delivered uniformly at 0.1 Gy/hr to the body over the first day following the accident, with no appreciable internal burden of radionuclides. For this dose rate, the median lethal dose is expected to be about 3.7 Gy (see Section 1.2.3). Thus, the 1.85 Gy cumulative dose when converted to the dose X in units of median lethal dose, is 1.85/3.7 = 0.5 or one-half of a median lethal dose. Also, suppose that during the next 3 days the same individual receives an additional 2.4 Gy delivered with an average dose rate of 0.04 Gy/hr. For protracted exposure at 0.04 Gy/hr, the median lethal dose is estimated to be about 4.8 Gy (see Section 1.2.3). When expressed in terms of the dose X, this added dose is 2.4/4.8 = 0.5; also one-half of a median lethal dose. The total dose X received over the 4 day exposure period is therefore 0.5 + 0.5 = 1, which corresponds to a median lethal dose. Thus for this individual, the 1.85 Gy + 2.4 Gy (total 4.25 Gy) would have given a 50 percent chance of dying from acute effects, assuming no medical treatment was administered.

It has been demonstrated (Scott et al., 1988a) that use of this hazard-function approach leads to predictions in good agreement with data for sheep (Krebs and Jones, 1975; Still et al., 1969) exposed to varying dose rates.

2.1.2.3.3 Modeling Medical Treatment Effect

State-of-the-art antibiotic therapy, platelet, blood and serum (gamma-globulin) transfusions, and good hospital nursing practice were reported

by Gus'kova (1987) to ameliorate the acute hematopoietic syndrome in victims of the Chernobyl nuclear power plant accident. It is estimated from animal data that supportive treatment increases the median lethal dose by a factor of about 1.5 (Vriesendorp and van Bekkum, 1984; Perman et al., 1962; WASH 1400, 1975).

Example: Suppose that a second individual was exposed to the same doses over the same time periods as in Example 1. However, this individual received supportive medical treatment. His dose X would be calculated as X = 1/1.5 = 0.667, or 66.7 percent of a median lethal dose. The protection factor of 1.5 is based on extrapolations from animal data (see Section 1.2.3.4). This dose is slightly above the judgmental threshold value of 0.5 (50 percent of median lethal dose) for death from the hematopoietic mode. Based on Equations 1 and 2, with V = 6[a] for the hematopoietic mode of lethality, the individual would therefore have a calculated risk of death of:

$$\text{Risk} = 1 - \exp[-0.693(0.667)^{6}] = 0.06 \qquad (3)$$

as compared to a risk of 0.5 in the absence of supportive treatment. The implication is that substantial benefit from the supportive treatment would be expected. Such a dramatic effect is due to the steepness of the dose-effect curve for acute lethality. A small change in effective dose can lead to a substantial change in risk. With dose X less than 0.5, an individual would be expected to incur no risk of hematopoietic death.

The 0.5 value for the threshold is based on an analysis of a large data base for laboratory mammals exposed to both high- and low-LET radiations at a variety of dose rates (Jones, 1981).

2.1.2.3.4 Competing Modes of Death

For some nuclear accident scenarios, internal dose to critical organs other than the bone marrow can also lead to loss of life from early effects. The internal irradiation is due to inhaled and ingested radionuclides. A large internal radiation dose to the lung can cause lethal radiation pneumonitis. The following example illustrates this point:

Example: Suppose that a third individual less than 40 years of age was exposed to a very high external gamma-ray dose (6.5 Gy) to the bone marrow at a dose rate of 0.5 Gy/hr during the first day. Thereafter, he had no external dose due to evacuation from the region, but inhaled a substantial lung burden of beta-emitting radionuclides. For exposure at

---

[a]Based on the ratio LD_{90}/LD_{10} extrapolated from animal data to a 70 kg mammal (Morris and Jones, 1988a) and the Weibull model (Scott et al., 1988a).

0.5 Gy/hr, the D_{50} is estimated in Section 1.2.3 to be 3.1 Gy to the bone marrow. This external dose would correspond to a dose X = 6.5/3.1 or 2.1. For this individual, the risk of death from the hematopoietic mode would be calculated as:

$$\text{Risk} = 1 - \exp[-0.693(2.1)^6] = 1.0 \qquad (4)$$

This individual might require bone marrow transplantation to survive the hematopoietic mode of death, although the range of doses where bone marrow transplantation is beneficial is uncertain. Suppose that his total internal and external dose X to the lungs was 1. This could occur, because for lung, an external 6.5 Gy dose delivered at 0.5 Gy/hr would correspond to a dose X = 6.5/70 = 0.093, which is considerably less than 1. For exposure of the lung at 0.5 Gy/hr, the D_{50} is estimated in Section 2.2.5 to be 70 Gy. Although this individual might be rescued from the hematopoietic mode of death if he were given bone marrow transplantation and/or supportive treatment, there would still remain about a 50 percent chance of death from radiation pneumonitis. Had the individual been a person over 40 years of age, he would have been expected to be about twice as sensitive to irradiation (see Section 2.2.5). His dose X would therefore have been calculated to be twice as large, i.e., X = 2, or twice the median lethal dose. As shown in Table 2.1, this individual would be expected to die from radiation pneumonitis even if the individual survived lethal injury to the bone marrow. Other complications could also arise for individuals receiving bone marrow transplantation therapy for supralethal radiation doses including lethal graft vs. host disease and lethal interstitial pneumonitis caused by viral, protozoal or fungal infections. The lung model used in this report only accounts for deaths from radiation pneumonitis.

2.1.2.4 Effects 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 sigmodial-type function would lead to about the same number of expected deaths. Other models were considered (Jones, 1981; Goldman and Raabe, 1977; Wells, 1976; Filipy et al., 1980; Morris and Jones, 1988a) including the tolerance-dose-distribution models (logit, gamma, extreme value, normal, etc.). When modeling acute lethality after prompt exposure, the linear probit or logit model may actually perform better in the low and very high-risk regions than the two-parameter Weibull models (Morris and Jones, 1988a). However, the two-parameter Weibull model is easy to implement and has certain advantages in accounting for dose-rate effects (Scott et al., 1988a, 1987).

2.2 Organ-Specific Effects and Models

The objectives of the following sections are to discuss briefly the effects of uniform low-LET irradiation of various organs and to estimate

Table 2.1

Risk of Death as a Function of Dose X to the Lung in Units of the D_{50}

Normalized Dose X[a]	Risk
0	0
0.25[b]	0
0.5	0[c]
0.75	0.15
1.00	0.5
1.25	0.88
1.50	0.99
1.75	1
2.00	1

[a]A dose X = 1 corresponds to a median lethal dose; it is assumed that the effective dose to the lung is due to internal irradiation. For internal exposure at 0.1 Gy/hr, the median lethal dose is estimated to be 320 Gy.

[b]Doses below threshold dose of 0.5 lead to no risk.

[c]A dose X = 0.5 represents the current central estimate of the threshold dose.

the D_{50}, threshold and shape parameter for most of the quantal effects modeled.

Risk models are developed for effects in specific organs, although radiation exposures usually involve several organs. This approach is used because it allows one to estimate risks when the doses and dose-rate patterns for critical organs differ.

Interaction of effects among organs occurs in response to radiation injury. However, available data do not permit examination of these effects.

2.2.1 Effects of Total-Body Irradiation

2.2.1.1 Systemic Effects

Systemic response to irradiation is related to tissue injury. Irradiated tissue has been described on the basis of whether renewal cells and functional cells occur at different places in the tissue (Thames and Hendry, 1987). Tissue in which the cell populations responsible for renewal and function are located at different places are called hierarchical (type-H) tissue (Thames and Hendry, 1987); tissue in which some functional cells are capable of renewal are called flexible (type-F) tissue. Examples of type-F tissue include lung, kidney, liver, and spinal cord.

Most of the tissues that demonstrate acute effects soon after irradiation are hierarchical in structure (Thames and Hendry, 1987). Acute lethality from the hematopoietic mode after total-body irradiation results from injury to the type-H bone marrow tissue. Radiation pneumonitis and pulmonary fibrosis results from injury to type-F tissue in the lung. For type-F tissue, acute effects may occur several months after a brief exposure or after more than a year of protracted exposure (Scott et al., 1987).

The systemic 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; Lushbaugh et al., 1967; UNSCEAR, 1982; Barabanova et al., 1986; Young et al., 1987). 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 who received total-body exposure.

The timing and occurrence of symptoms induced by total-body irradiation are related to radiation dose. After very high doses (greater than 20 Gy), received in a short period of time, the predominant symptoms 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 even when antishock therapy is given;

it is related to injury to the cardiovascular systems and secondarily to the nervous systems. At lower doses (6 to 20 Gy), the predominant symptoms are overwhelming sepsis and toxemia. Nausea, vomiting, diarrhea, dehydration and death should also occur. At even lower doses (2 to 6 Gy), signs of infection and bleeding may occur that are related to hematopoietic depression resulting in a decrease of blood cell numbers. 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 by depression of blood cell formation. Death is due to infection, toxemia secondary to agranulocytosis, hemorrhage due to thrombocytopenia, and immunosuppression.

2.2.1.2 Prodromal Syndrome

The prodromal syndrome is a group of symptoms and signs of acute gastrointestinal and neuromuscular effects that begin to occur within hours after brief irradiation (Langham, 1967). The gastrointestinal symptoms include anorexia, nausea, vomiting, diarrhea, intestinal cramps, salivation, and dehydration (Young, 1986). Anorexia, nausea, and vomiting occur as part of the earliest signs of radiation sickness. The neuromuscular symptoms include fatigue, listlessness, apathy, sweating, and headache. After supralethal doses, hypotensive shock occurs due to vascular damage. At the median lethal dose, the principal symptoms of the prodromal reaction are anorexia, nausea, vomiting and fatigue. Early diarrhea, fever, and hypotension occur primarily in victims who have received supra-lethal doses (Langham, 1967). Early diarrhea does not occur in more than about 10 percent of irradiated persons unless doses to the abdomen exceed about 10 Gy. Delayed diarrhea, associated with the manifest phase of radiation illness, does occur in a higher percentage of individuals at doses to the abdomen from about 2 to 3.5 Gy. Prodromal symptoms can occur without subsequent radiation-induced death or severe illness (Andrews et al., 1980; Baverstock and Ash, 1983).

For emesis, the time of onset, severity, duration and recovery vary according to the magnitude of the dose, dose rate and region of the body irradiated (Borison, 1957; Court-Brown, 1953; Young, 1986). The symptoms can be produced by exposures of the abdomen, thorax, or head but not by exposure of the extremities. Irradiation of the upper mid portion of the abdomen (over the stomach) elicits the responses with the least dose, whereas massive 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. In monkeys, high doses cause incapacitation which suppresses vomiting (Middleton and Young, 1975). The extent to which a radiation dose delivered to the stomach from an internal beta-emitting radionuclide would induce prodromal symptoms is uncertain. No reliable data with internal emitters is currently available.

The prodromal syndrome is the result of a parasympathetic neurogenic response to irradiation. It is generally considered that radiation-induced vomiting occurs through effects on the chemoreceptor trigger zone and vomiting center in the medullary nuclei of the brain. These effects may result from humoral factors released from damaged tissue and/or activation of peripheral afferent nerves of the stomach.

2.2.1.3 Dose-Effect Relationships

In this chapter, dose-effect relationships for the prodromal syndrome are focused on two signs: vomiting and diarrhea. 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). This newer information is based on a retrospective study of 2000 patients given therapeutic total-body irradiation. Estimates of the median effective doses for the symptoms of vomiting and diarrhea for brief exposures are given in Table 2.2. The D_{50} is lower for vomiting (2 Gy), higher for diarrhea (3 Gy). The median effective doses for protracted exposures are also given in Table 2.2. Protraction of the dose increases the median effective dose.

A dose-effect relationship for prodromal vomiting after brief exposure is shown in Figure 2.1 and is mainly based on the same data used in the Reactor Safety Study (WASH 1400, 1975). The median effective dose derived by Lushbaugh (1982) for diarrhea was added to the figure.

Estimates of the shape parameter, V, and thresholds are also summarized in Table 2.2. These are based on information from Lushbaugh (1967, 1982), Langham (1967) and the Reactor Safety Study (WASH 1400, 1975).

2.2.2 Central Nervous System

Relatively high radiation exposures can cause effects in the brain including the acute reactions of incapacitation and acute encephalopathy, as well as the delayed reactions of subacute demyelination and late encephalopathy. Spinal cord effects include acute transverse myelitis, and chronic progressive myelopathy. Peripheral neuropathy may also occur. A detailed and definitive analysis of radiation effects on the human nervous system as it relates to radiation therapy, is provided by Gilbert and Kagan (1980).

Data on the nervous system effects come primarily from the radiation therapy literature and experimental animal data. The emphasis in the clinical reports is on minimization of therapeutic complications, thus the results focus on the lower portion of the dose-response curve. Table 2.3 indicates that the minimum dose for even transient symptoms from central nervous lethal effects may require larger doses. These doses are well into the supralethal range when delivered to the whole body instead of to a small part of the brain or even the whole head.

Table 2.2

Median Dose Estimates (D_{50}) and Response Curve Parameter (V) for Prodromal Symptoms After Total Body Irradiation[a]

	Vomiting		Diarrhea	
Parameter	Brief Exposure[b]	Protracted Exposure[b]	Brief Exposure	Protracted Exposure
D_{50} (Gy)	2	5	3	6
Lower Bound	1.5	3.8	2.4	4.8
Upper Bound	2.5	6.2	3.8	7.5
Threshold (Gy)	0.5	1.5	1	2.5
Shape	3	3	2.5	2.5

[a]Judgmental values obtained by working group from data of Lushbaugh et al. (1982) for 2,000 patients given total-body irradiation. Uncertainties involved assumed to be accounted for by upper and lower bounds selected for D_{50}.

[b]Brief implies dose rates equal to or greater than 0.06 Gy/hr. Protracted implies dose rates below this range. The parameter estimates for D_{50} may not be applicable to very high dose rates as can occur with nuclear weapons.

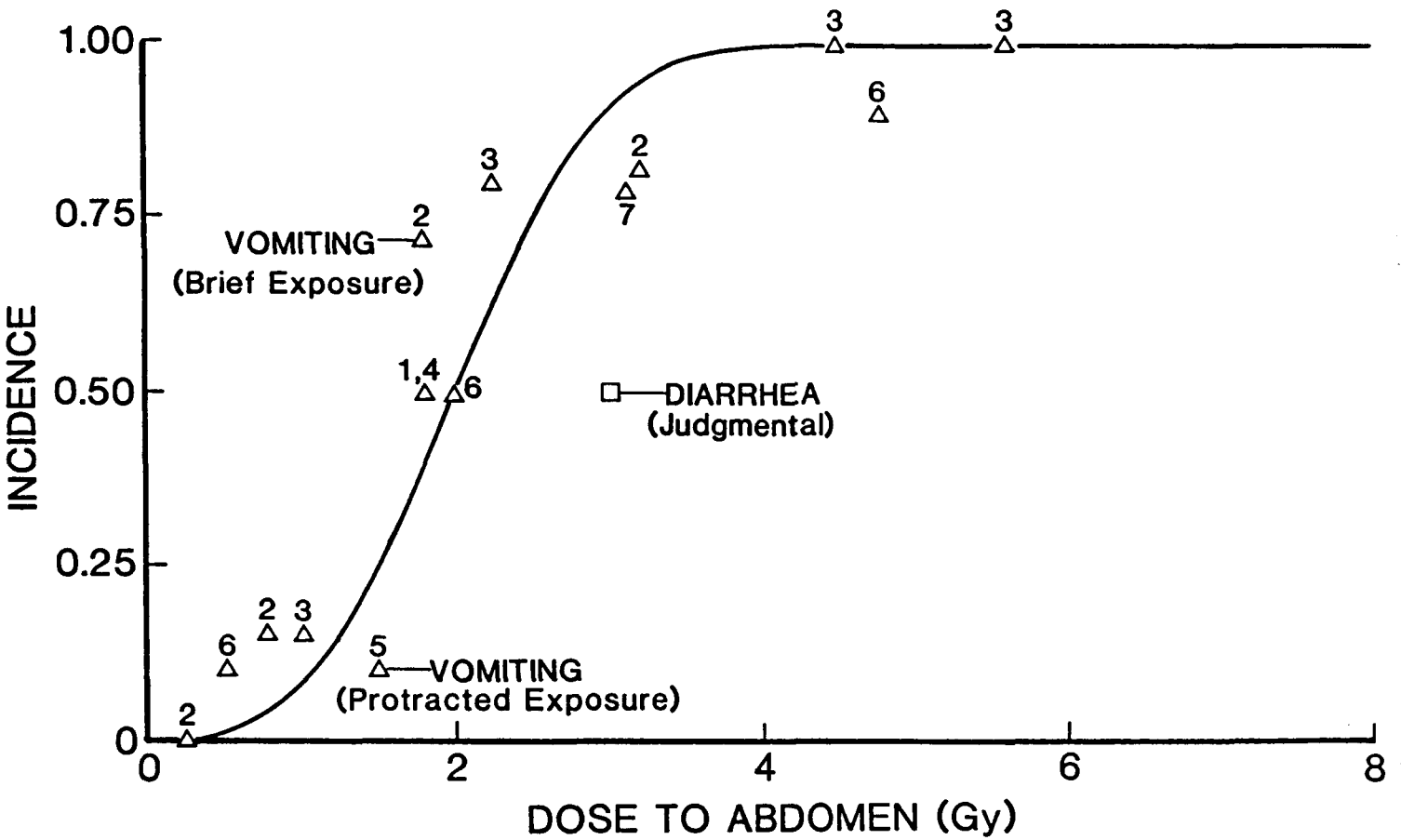

Figure 2.1. Dose-Effect Relationship for the Incidence of Prodromal Vomiting Within 2 Days of Brief Irradiation. Based on information provided in the Reactor Safety Study (WASH 1400, 1975) with additional data from Lushbaugh (1982) based on 2,000 patients given therapeutic total-body irradiation. The median effective dose given by the open square represents diarrhea. Origin of other data: 1, Lushbaugh (1982); 2, accident exposure cases, Langham (1967); 3, accident exposure cases (Thomas and Wald, 1959; updated); 4, therapy patients (Thomas, 1971); 5, Rongelap fallout cases, protracted 50-hour exposure (Langham, 1967); 6, average of normal arithmetical and log-normal values given in Langham (1967); 7, Toronto-therapy cases (11/14) with Gravol pretreatment (WASH 1400, 1975).

Table 2.3

Radiation Dose Required to Produce Effects Related to the Central Nervous System[a]

Brain	Effective Dose (Gy) 5%	50%	95%
Acute Reactions			
Incapacitation	6-7[b,c]	17[c]	~50[c]
Acute encephalopathy	>50-80[d]	--	--
Delayed Reactions			
Subacute demyelination	60-70[e]	--	--
Late encephalopathy	10-60[f]		

[a]Unpublished literature review by Dr. Nield Wald (1987).

[b]Hindo et al. (1970).

[c]Young (1986).

[d]60-80 Gy at 2 Gy/day (Sheline, 1980; Leibel et al., 1987); 50 Gy at 1.7-1.8 Gy/day (Hoffman et al., 1979).

[e]Sheline (1980).

[f]33 Gy/10 days (Lindgren, 1958), 52 Gy/15 d (Lindgren, 1958), 10-11 Gy (Cohen and Creditor, 1989), 16-20 Gy (Hoffman et al., 1979), 10 Gy (Sheline, 1980), 60 Gy/49 days (Marks and Wong, 1985), 60 Gy/42 days (Leibel and Sheline, 1987).

Thus, dose-response curves for central nervous system effects were not developed.

2.2.3 Bone Marrow

2.2.3.1 Nature of Effects

The effects observed after bone marrow irradiation result from killing blood cell precursors (stem cells) in the marrow (Bond et al., 1965; UNSCEAR, 1982). The bone marrow is the source of most circulating blood cells, the granulocytes, erythocytes, and platelets. The response of the peripheral blood elements depends upon their normal turnover time, with the exception of lymphocytes. Lymphocytes are generally very radiosensitive and die soon after irradiation, undergoing interphase, rather than mitotic, death. A depletion of blood lymphocytes is seen within hours after total body irradiation, whereas the decrease in platelets and granulocytes is delayed for several days. The onset of a decrease in erythrocytes occurs slowly over weeks, but can be accelerated by hemorrhage. If the depression in peripheral blood cells is severe, an individual may die from infection because of deficient numbers of granulocytes, or hemorrhage because of deficient numbers of platelets combined with damage to the vasculature. However, unless the total number of marrow stem cells is depressed below some critical level, the numbers of peripheral blood cells will return to normal and the individual will survive.

In a recent workshop entitled "Short-Term Health Effects of Reactor Accidents: Chernobyl," a number of important conclusions were arrived at related to implication of peripheral blood cellularity after irradiation (Fliedner, 1986):

1. For all practical purposes, the probability of survival will depend on hemopoietic stem cell survival and the probability that they will undergo self-renewal and differentiation into the major blood cell lineages.

2. Lymphopenia occurring within a few hours and becoming maximum between 48 to 72 hours indicates a significant radiation exposure.

3. When irradiation is combined with trauma or third-degree burns, neutropenia and thrombopenia may be enhanced and lead to a substantial increase in the possibility of death from sepsis and/or hemorrhage.

2.2.3.2 LD_{50} For Man

As indicated in Table 2.4, the LD_{50} for hematopoietic death in man is not precisely known for either brief or protracted total-body exposure to low-LET radiation. Estimates for brief exposure at high dose rates range

Table 2.4

Estimates of LD_{50} for Total-Body Irradiation of Man for Brief or Protracted Exposure to External Low-LET Photon Radiation

Exposure Category[a]	Type of Dose	Exposure Time	LD_{50} (Gy)	Comment	Reference
Brief	Bone Marrow	Short	3	Judgmental value for man; based on limited data and extrapolation from animal data	Bond et al., (1965); Warren and Bowers (1950); Vriesendorp and van Bekkum (1984)
Brief	Epigastric	Short	2.8	Mostly very ill patients; adjustment for non-radiation induced effects	Lushbaugh et al. (1967)
Brief	11 cm below surface of body	0-1 day	2.86	Report of Space Radiation Study Panel based largely on very ill patients	Langham et al. (1967)
Brief	Bone marrow	Prompt	2.44	People exposed in their homes in Hiroshima, 1.54 Gy estimate of Rotblatt (1986) reevaluated based on DS86 dosimetry and new transmission factors; blast and burn injuries	Fujita et al. (1987)

[a]Brief implies exposure durations up to and including 1 day; protracted implies exposure over a time longer than 1 day. These definitions differ from those used in the text to distinguish low and high dose rates.

Table 2.4

Estimates of LD_{50} for Total-Body Irradiation of Man for Brief or Protracted Exposure to External Low-LET Photon Radiation (Continued)

Exposure Category[a]	Type of Dose	Exposure Time	LD_{50} (Gy)	Comment	Reference
Brief	Bone marrow	Short	4.8-5.1	Vinca accident victims; both supportive and intensive treatment provided to some[b]	Mole (1985)
Brief	Bone marrow	Short	4.5	Judgmental value used in this chapter for supportive treatment category	Vriesendorp and van Bekkum (1984)
Brief	Total body	Short	6	Chernobyl accident; both supportive and intensive treatment provided to some; severe skin burns; see Figure 1.6 for our estimation of LD_{50}	Gus'kova (1987)
Brief	Bone marrow	1 day	3.4	Judgment provided in Reactor Safety Study	WASH 1400 (1975)
Protracted	Bone marrow	2 days	3.5	Marshall Islanders exposed to fallout and extrapolations from animal data	Cronkite (1982)

[a]Brief implies exposure durations up to and including 1 day; protracted implies exposure over a time longer than 1 day. These definitions differ from those used in the text to distinguish low and high dose rates.

[b]The single death observed at Vinca was not the result of uncomplicated bone marrow damage and doses may have been nonuniformly distributed (Baverstock, 1985).

Table 2.4

Estimates of LD_{50} for Total-Body Irradiation of Man for Brief or Protracted Exposure to External Low-LET Photon Radiation (Concluded)

Exposure Category[a]	Type of Dose	Exposure Time	LD_{50} (Gy)	Comment	Reference
Protracted	11 cm below Surface of body	1-7 days	3.1	Report of Space Radiation Panel based largely on very ill patients	Langham et al. (1967)
Protracted	Bone marrow	1 week	4.5	Judgment provided by Office of Technology Assessment	OTA (1980)
Protracted	Bone marrow	1 month	6.0	Judgment in British Institute of Radiology Report	BIR (1982)

[a]Brief implies exposure durations up to and including 1 day; protracted implies exposure over a time longer than 1 day. These definitions differ from those used in the text to distinguish low and high dose rates.

from 2.4 Gy to 5.1 Gy. When estimates based on individuals that received significant medical treatment are excluded, the range reduces to 2.4 to 3.4 Gy with a midrange estimate of 2.9 Gy or approximately 3 Gy.

2.2.3.3 Influence of Dose Rate on LD_{50}

Although human data provide a basis for estimating the LD_{50} for a brief exposure, models developed from experimental animal data are usually used to predict the influence of dose rate.

Comprehensive analyses have been conducted recently on acute lethality data for irradiated humans and laboratory animals (Jones et al., 1986a, 1986b; Morris and Jones 1988a, 1989; Scott et al., 1988a). The analyses have led to development of new dose rate models. The animal data were derived from a number of experimental designs. A covariate model was developed for estimating the LD_{50} as a function of body weight and exposure rate (Morris and Jones, 1989). With the Covariate Model, the LD_{50} projections for brief exposure of a 70 kg mammal (surrogate for man) at 0.6 Gy/hr was 3.0 Gy (1.7 to 5.4 Gy). Values within parentheses represent 95 percent prediction limits. Based on animal data in Figure 2.2, the LD_{50} is expected to vary only a small amount as the dose rate increases above about 0.6 Gy/hr (1 CGy/min). It is our judgment that the 3 Gy extrapolated estimate of the LD_{50} is therefore a reasonable approximation for dose rates equal to or greater than about 0.6 Gy/hr.

Extrapolation from animal data, based on the concentration of hematopoietic stem cells in the bone marrow would also place the LD_{50} for man at about 3 Gy. The 3 Gy value applies to individuals not receiving medical treatment and to a dose rate to the bone marrow equal to or greater than about 3.6 Gy/hr (Vriesendorp and van Bekkum, 1984).
Research has also led to the use of animal data to obtain an empirical Dose Rate Model (Scott et al., 1988a; Scott, 1987) for characterizing the relationship between the LD_{50} and the dose rate of low-LET radiation. The Dose Rate Model is applicable to a wider range of dose rate than the ORNL Covariate Model (Morris and Jones, 1989). Both models lead to similar results at intermediate dose rates (Scott et al., 1988a). The mathematical form of the Dose Rate Model is as follows:

$$\theta \text{ (dose rate)} = \theta_1/\text{(dose rate)} + \theta_\infty \qquad (5)$$

where θ (dose rate) represents the dose-rate-dependent median lethal dose; θ_1 and θ_∞ are model parameters that can be estimated from the data. The parameter θ_∞ represents the high dose rate anchor (i.e., asymptotic value) of the median lethal dose expected to occur when recovery during irradiation is essentially eliminated by the high-dose-rate exposure. For man, a judgmental central estimate of θ_∞ is 3 Gy to the bone marrow based on information provided in Table 2.4. The quotient θ_1/(dose rate) represents the increase in the median lethal dose due to recovery and

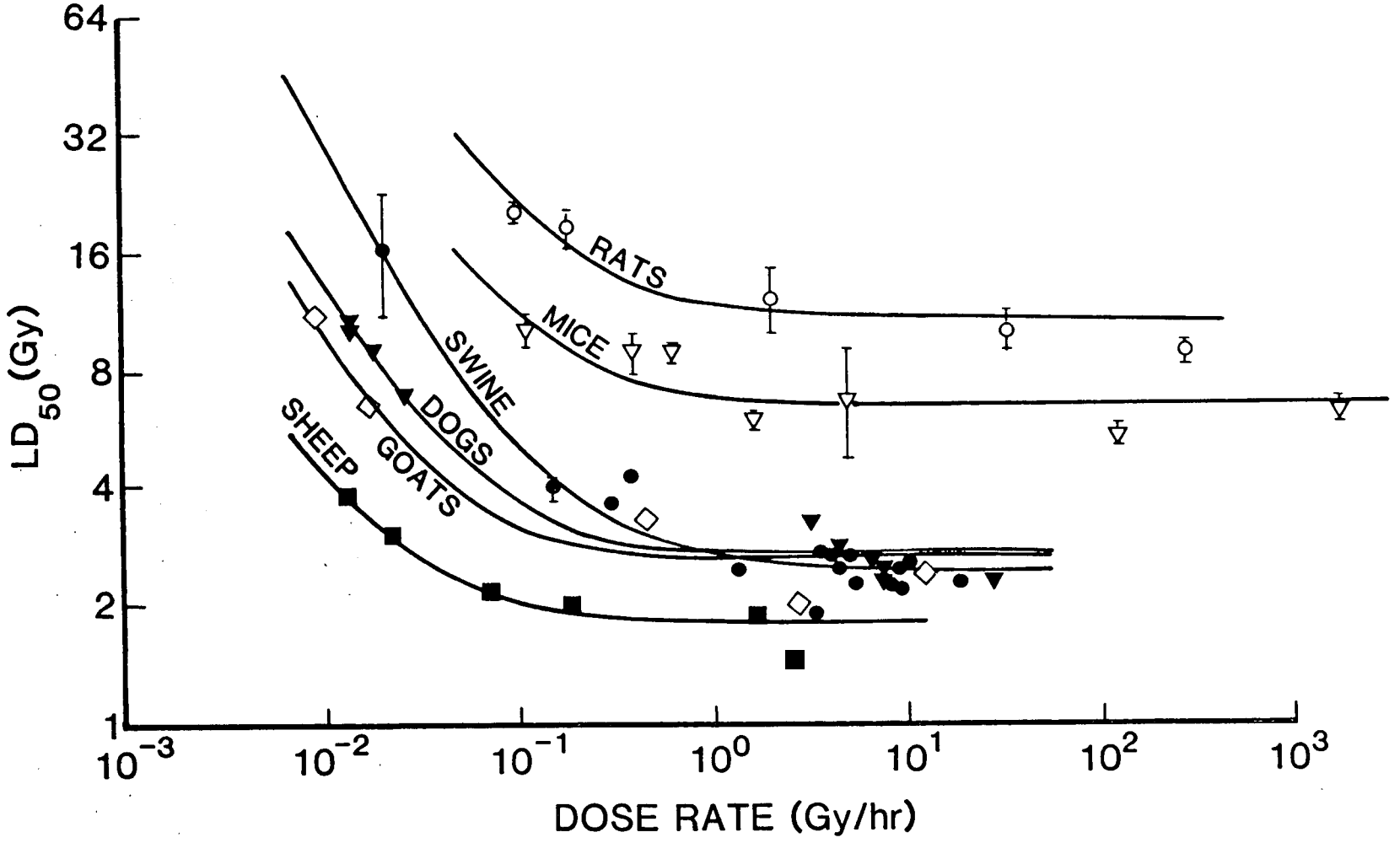

Figure 2.2. Median Lethal Dose vs. Dose Rate for Various Mammals Exposed Uniformly Over the Body to High-Energy Photons (MV range X-rays or ^{60}Co gamma rays) (Scott et al., 1988a)

repair during protracted irradiation. The Dose Rate Model is based on the animal data shown in Figure 2.2.

To estimate the second parameter Θ_1, the high-dose-rate anchor Θ_∞ (the LD_{50} at high dose rates) was fixed at 3 Gy and data for the Mexican family exposed in their home to ^{60}Co gamma rays (Lushbaugh, 1974) and for Japanese fishermen exposed to fallout radiation (Kumatori et al., 1980) were used. This led to an estimate of 0.072 Gy^2/hr (12 rad^2/min) for the parameter Θ_1 (Scott, 1987). It is shown in Figure 2.3 that the model is in reasonable agreement with data and judgmental values for man; other data and judgments shown in Figure 2.3 at low and moderate dose rates were excluded when estimating Θ_1 because of the likelihood of large systematic errors in the data and judgments. The data points for the Mexican family exposed to gamma radiation and Japanese fishermen exposed to fallout from an atmospheric nuclear weapons test do not represent LD_{50}s, but represent calculated total-body doses. The member of the Mexican family with the smallest dose survived. The other four members died. None of the Japanese fishermen died from acute effects of irradiation.

Because the Dose Rate Model is applicable to a wider range of dose rates than the Covariate Model, and is in agreement with the Covariate Model at intermediate dose rates, we find the Dose Rate Model preferable to the Covariate Model for estimating the consequences of nuclear reactor accidents where a large percentage of the radiation dose of interest can arise from protracted exposures.

Using the model with Θ_1 = 0.072 Gy^2/hr and Θ_∞ = 3 Gy, and a Weibull risk-vs.-dose model (Scott et al., 1988a) with the shape parameter of 6, based on the ratio LD_{90}/LD_{10} extrapolated from animal data to a 70 kg mammal (Morris and Jones, 1989), 3 deaths were expected among the Mexican family exposed to ^{60}Co gamma radiation (4 were observed) and less than 1 was expected among the 23 Japanese fishermen exposed to fallout radiation (the single death that occurred was not related to irradiation).

2.2.3.4 Influence of Medical Treatment

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; BNL 52030, 1986).

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

Supportive treatment includes hospitalization with routine isolation procedures (i.e., not including laminar airflow), electrolyte replacement, administration of blood products (especially fresh platelets),

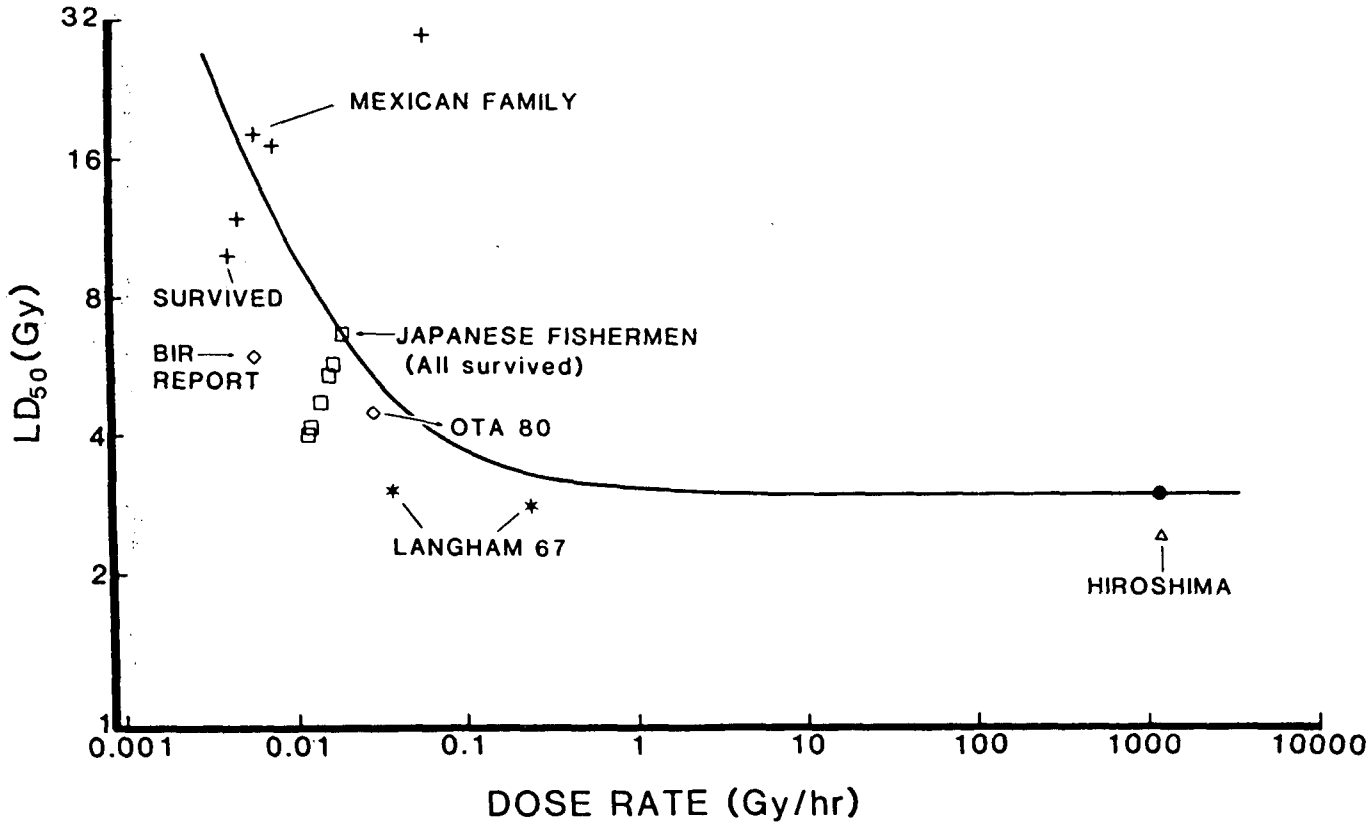

Figure 2.3. Median Lethal Dose vs. Dose Rate for Man. Based on Dose Rate Model (Scott, 1987) with high dose rate anchor of 3 Gy (Vriesendorp and van Bekkum, 1984; Bond et al., 1965; Warren and Bowers, 1950) and parameter θ_1 equal to 0.072 Gy^2/hr. Sources of data and judgmental values: LANGHAM 67: Langham's (1967) two estimates based on linear probit model for exposure for 0-1 day and 1-7 days. HIROSHIMA: Rotblat's (1986) estimate for Hiroshima with LD_{50} dose at 892 meters from hypocenter; dose estimate modified based on DS86 dosimetry (Ka87) and new transmission factors (Fujita et al., 1987). MEXICAN FAMILY: Mexican family unknowingly exposed intermittently in their home to ^{60}Co gamma radiation (Lushbaugh, 1974); 4 out of the 5 died. A factor of 0.0073 was used to convert R to Gy. Values plotted represent midrange of estimated individual doses rather than values for median lethal dose. JAPANESE FISHERMEN: Seven of the 23 Japanese fishermen (Kumatori et al., 1980) exposed to fallout gamma radiation that had estimated total-body doses greater than 4 Gy; 0/7 died from marrow-syndrome mode. Values plotted represent midrange of estimated individual total-body external dose rather than median lethal doses. Sixteen other fishermen with lower doses also survived the acute radiation syndrome. OTA 80: Judgment of LD_{50} provided by the Office of Technology Assessment (OTA, 1980) for a 1 week exposure period. BIR REPORT: Judgment of LD_{50} provided by the British Institute of Radiology (BIR) for a 1 month exposure period (BIR, 1982). CLOSED CIRCLE (•): Closed circle at high dose rate end represents high dose rate anchor θ_∞ = 3 Gy, based on central estimate obtained from information in Table 2.4.

treatment with broad-spectrum antibiotics, antifungals and antivirals and parenteral feeding. Intensive treatment includes, in addition to supportive treatment, extraordinary procedures such as bone marrow transplantation and the use of colony stimulating factors. The term "minimal treatment" indicates the absence of any of these measures. Basic first aid in a clean environment is considered minimal treatment.

Medical treatment has been shown to increase the survival of irradiated individuals (Andrews et al., 1980). However, the treatments described here are not intended as guides to physicians but rather as planning aids for calculating expected illnesses and deaths after radiation accidents.

Data from studies of the victims treated following the Chernobyl accident provide insights on the influence of medical treatment on survival (Gus'kova, 1987; Young, 1988). Six persons received human fetal liver transplants which were unsuccessful. Five of these patients had severe skin and intestinal lesions. Transplantation of allergenic bone marrow was carried out 13 times; 2 recipients survived. Seven recipients died between 2 and 19 days after transplantation (15 to 25 days after irradiation) from acute radiation lesions of the skin, intestine and lungs. Of 6 patients that did not have severe injury to the skin and intestine, and whose total-body dose estimates were in the range 4.3 to 10.7 Gy, 2 survived after rejecting allogenic bone marrow injection. Their doses were estimated to be between 5.8 to 9.0 Gy.

Four patients died from mixed viral-bacterial infections 27 to 29 days after allogenic bone marrow transplantation (Gus'kova, 1987). Two of the deaths occurred in spite of well-functioning grafts. Their total-body doses were estimated to be 5.0 to 7.9 Gy and 5.8 to 6.0 Gy, respectively. The other 2 deaths occurred after early rejection (14 to 17 days). The total-body doses were estimated for these patients to be 4.3 and 10.7 Gy.

The observation of LD_{50} of about 6 Gy based on data for heavily irradiated victims of the Chernobyl accident (Fig 2.4) and Weibull model with the shape parameter constrained to be 6 indicates that supportive treatment may have increased the median lethal dose assuming that radiation doses were not overestimated.

A substantial benefit of supportive medical treatment has also been observed in dogs after total-body low-LET irradiation (Perman et al., 1962; Sorensen et al., 1960). 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. The results indicate that about a 50 percent increase in the median lethal dose might be achieved by treatment. The 50 percent increase corresponds to a protection factor of about 1.5 provided by the supportive treatment. A protection factor of about 1.5 was also extrapolated to man from data for supportive treatment of dogs and monkeys after total-body irradiation (Vriesendorp and van Bekkum, 1984). With supportive treatment, the LD_{50} for man was extrapolated to be 4.5 Gy, and without treatment 3 Gy.

Similar results have been obtained more recently in studies with dogs following mixed neutron-gamma whole-body irradiation (MacVittie, 1984) where a protection factor of about 1.3 was attributable to supportive treatment.

Assuming the protection factor provided by supportive treatment to be in the range 1.3 to 1.5 would place the LD_{50} for hematopoietic death in man in the range 3.1 to 5.1 Gy, for a brief uniform exposure of the total body to gamma radiation. The estimated LD_{50} of about 6 Gy derived from the Chernobyl data in Figure 2.4 is above the 3.1 to 5.1 Gy range suggesting that radiation doses for the Chernobyl data may have been overestimated or that the sophisticated treatment provided to the accident victims was more protective than the treatment provided in experimental studies with animals.

Relevant data published between 1981 and 1987 that dealt with bone marrow transplantation in combination with radiation and chemotherapy were recently reviewed.[a] The data and references are summarized in Tables 2.5 and 2.6. A selection was made among the reports based on sufficiency of pertinent information, such as 60-day survival, as well as a desire to diversify diseases, ages, radiation sources, doses and dose rates. Most dealt with treatment of various forms of leukemia, with two dealing with the preleukemic stage, one with polycythemia vera, and another with multiple myeloma. Others concerned non-Hodgkin's lymphoma, renal failure and kidney transplanta- tion. Major competing modes of death were graft vs. host disease and interstitial pneumonitis. The data are consistent with a median lethal dose in excess of 10 Gy for those receiving bone marrow transplantation. For a 10 Gy dose, 85 to 90 percent survival is indicated. The data are also consistent with the hypothesis of an additional sparing effect of fractionated exposure as compared to a single exposure.

In addition to total body irradiation, the predominant preconditioning therapy prior to bone marrow transplantation included Cyclophosphamide in most cases, with Methotrexate, Carmustine (BCNU), Cytosine Arabinoside (Ara-C) and Busulfan as less frequent additions.

The most dominant type of marrow graft was an allograft from an HLA-matched sibling or other relative. Autografts were also used in lymphoma patients, after processing to minimize reinoculation of tumor cells.

Model parameter estimates for minimal and supportive treatment are summarized in Tables 2.7 and 2.8. Upper and lower bound estimates are also provided. Information related to survival time is provided in Tables 2.9 and 2.10, for death from acute effects of irradiation.

2.2.3.5 Availability of Intensive Treatment

While it was concluded in WASH 1400 (1975) that there were 8 operating bone marrow transplant facilities in the U.S. and 12 more coming on line,

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[a]Unpublished literature review by Dr. Niel Wald (1987).

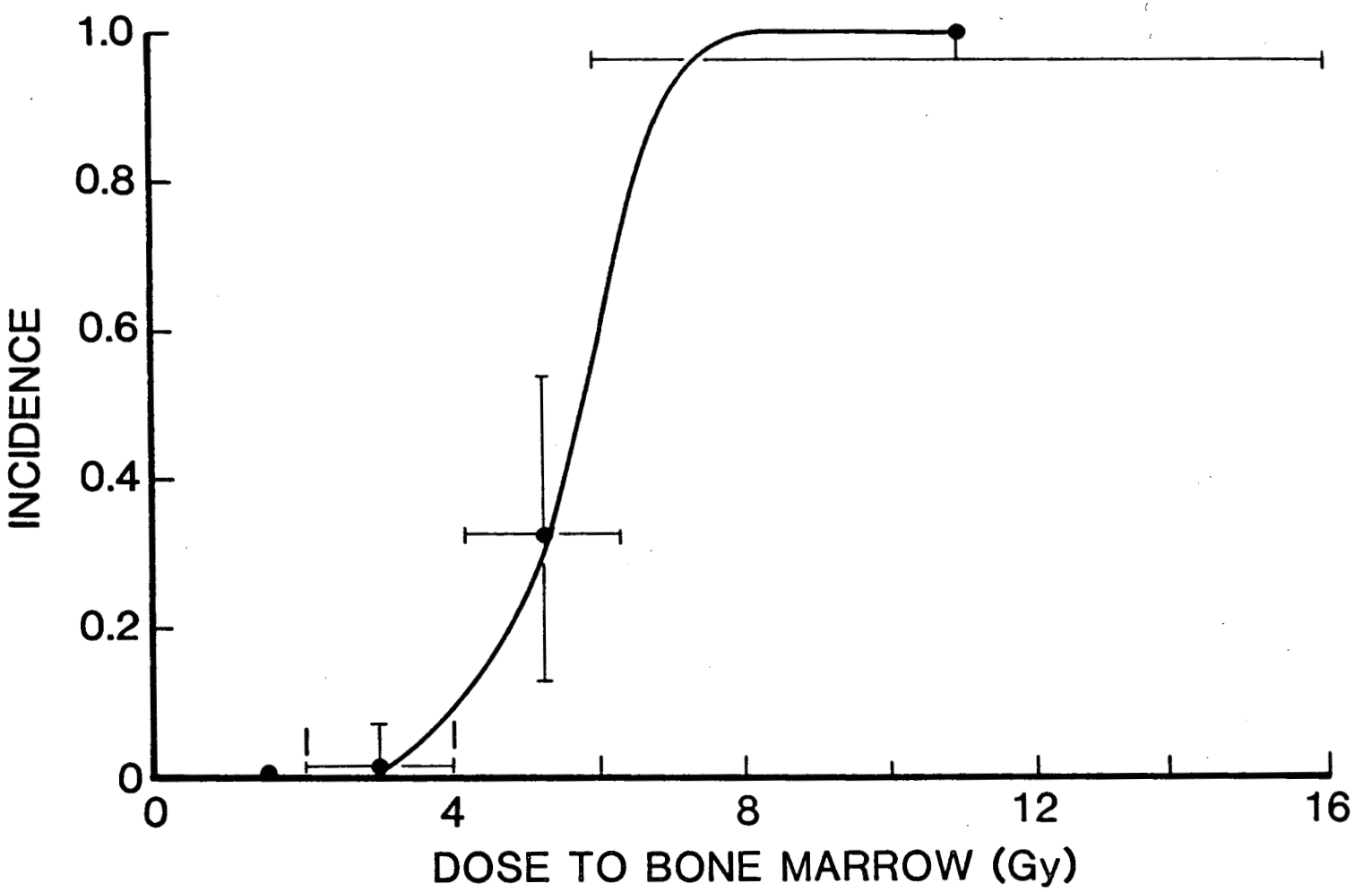

Figure 2.4. Dose-Effect Relationship for the Incidence of Acute Lethality Based on 115 Chernobyl Accident Victims Treated at the Specialized Station Hospital. Individuals received both supportive and intensive treatment (Gus'kova, 1987). The smooth curve is based on the Weibull model with a shape parameter of 6 and LD_{50} of 6 Gy. Vertical bars represent plus or minus 2 standard errors based on the binomial distribution. Horizontal bars represent the range of doses reported by Gus'kova (1987).

Table 2.5

Hematology Literature Review[a]
Total Body Irradiation: Single Exposure in Combination with
Bone Marrow Transplantation and Chemotherapy

No. of Cases	Primary Diagnosis	Dose Range (Gy)	Median Dose (Gy)	60 Day Survival (%)	60 Day Radiation-Related Mortality (%)	Reference
106	AML, ALL, CML	10	10	>73	<22	Tichelli (1986)
22	AML, ALL, CML	9	9	86	14	Kim et al. (1985)
8	ANLL, ALL, CML	7.5	7.5	100	0	Blume et al. (1987)
8	Multiple myeloma	9.5	9.5	88	13	Gahrton et al. (1987)
13	Malignant lymphoma	10	10	78	<19	Phillips et al. (1984)
7	Preleukemia	12-14	12	86	0	Applebaum et al. (1984)
34	ALL, ANLL	9.2-10	9.6	79	0	Fefer et al. (1981)
5	Non-Hodgkin's lymphoma	10-14	10	100	0	Applebaum et al. (1981)
8	Non-Hodgkin's lymphoma	10-17	10	50	38	Applebaum et al. (1983)
10	Burkitt's lymphoma, etc.	7.5	7.5	90	10	O'Leary et al. (1983)
18	ALL	10	10	83	17	Blume et al. (1987)
120	AML	8-12.5	10	>81	<19 (max)	Gale et al. (1982)

[a]Unpublished literature review by Dr. Niel Wald (1987). Abbreviations: AML = Acute myelocytic leukemia; ALL = acute lymphocytic leukemia; ANLL = acute nonlymphocytic leukemia; AL = acute leukemia; CML = chronic myelocytic leukemia; and CGL = chronic granulocytic leukemia.

Table 2.5

Hematology Literature Review[a]
Total Body Irradiation: Single Exposure in Combination with
Bone Marrow Transplantation and Chemotherapy
(Concluded)

No. of Cases	Primary Diagnosis	Dose Range (Gy)	Median Dose (Gy)	60 Day Survival (%)	60 Day Radiation-Related Mortality (%)	Reference
39	CML, 1st chronic stage	5-12	10	86		Speck et al. (1984)
56	CML, accelerated	5-13.2	8.5	68		Speck et al. (1984)
22	CML, blastic	4.5-15	10	40		Speck et al. (1984)
152	AML, in 1st complete remission	8-13	10	81		Bortin et al. (1983)
26	AML, 2nd-4th complete remission	8-13	10	76		Bortin et al. (1983)
22	AML, partial remission	8-13	10	72		Bortin et al. (1983)
23	AML, relapse	8-13	10	53		Bortin et al. (1983)
3	Multiple myeloma	10	10	100	0	Tura et al. (1986)
14	Non-Hodgkin's lymphoma	8	8	79	21	Verdonck et al. (1985)
49	Non-Hodgkin's lymphoma	8.5-12	8.5	96	4	Takvorian et al. (1987)
14	ALL, AML, CGL	7.5	7.5	100	0	Prentice et al. (1984)
59	AL, A & CML, ALL, myeloma, lymphoma	10	10	95	<5	Ringden et al. (1986)
TOTAL	838					

[a]Unpublished literature review by Dr. Niel Wald (1987). Abbreviations: AML = Acute myelocytic leukemia; ALL = acute lymphocytic leukemia; ANLL = acute nonlymphocytic leukemia; AL = acute leukemia; CML = chronic myelocytic leukemia; and CGL = chronic granulocytic leukemia.

Table 2.6

Hematology Literature Review[a]
Total Body Irradiation: Fractionated Exposure in Combination with
Bone Marrow Transplantation and Chemotherapy

No. of Cases	Primary Diagnosis	Dose Range (Gy)	Median Dose (Gy)	No. of Fractions	60 Day Survival (%)	60 Day Radiation-Related Mortality (%)	Reference
11	Renal failure	16.0-41.5	27.4	24-12	100	0	Sutherland et al. (1983)
12	ALM, ALL, CML	10	10	6	<73	<22	Tichelli (1986)
27	Preleukemia	10-14	12	6	78	22	Applebaum (1987)
39	ANLL, ALL, CML, CMMOL, Hodgkin's +	13.2	13.2	11	85	15	Blume et al. (1987)
6	Multiple myeloma	10-12	12	3-5	100	0	Gahrton et al. (1987)
32	AML, ALL, CGL, multiple myeloma	12	12	6	81	19	Herve et al. (1987)
14	Malignant lymphoma	12-16	14?	2/d x 3-4d	78	14	Phillips et al. (1984)
52	CML, 1st chronic phase	10-12	10	5-6	94	?	Goldman et al. (1986)
18	CML, accelerated, blastic, etc.	10-12	10	5-6	78	?	Goldman et al. (1986)
3	Non-Hodgkin's lymphoma	12-14	14	6-7	100	0	Applebaum et al. (1981)
12	Non-Hodgkin's lymphoma	12-17.5	15.8	6-7	58	33	Applebaum et al. (1983)
21	ALL	13.2	13.2	4	100	0	Blume et al. (1987)
20	Diabetic nephropathy	20-30	25	5/wk x 4 wks+	95	0	Waer et al. (1987)
108	Indolent lymphoproliferative d	1.5	1.5	2/wk x 5 wks	100	0	Jacobs and King (1987)
13	AML	8-12.5	10	2-6 x 1-6d	78	?	Gale et al. (1982)
49	Non-Hodgkin's lymphoma	8.5-12	12	2/d x 3	96	4	Takvorian et al. (1987)
28	CML, good-risk category	10-12	12	5-6	96	4	Apperley et al. (1986)
11	CML, poor-risk category	10-12	12	5-6	92	?	Apperley et al. (1986)
35	CML, good-risk category control	10-12	12	5-6	96		Apperley et al. (1986)
12	CML, poor-risk category control	10-12	12	5-6	92		Apperley et al. (1986)
17	ALL, 2nd remission	9.9 or 12	9.9	3	100	0	Bacigalupo et al. (1986)
16	ALL, chemotherapy-only controls	0	0	0	94	0	Bacigalupo et al. (1986)
18	A & CML, in remission or chronic	10-12	10	5-6	80	20	Goolden et al. (1986)
2	Polycythemia vera	10 Sv	10 Sv	--	100	0	Gmur et al. (1983)
TOTAL	579						

[a]Unpublished literature review by Dr. Niel Wald (1987). Abbreviations: d = Days, /wk = per week, wks = weeks, x 5 wks = over 5 weeks, etc; other abbreviations (AML, ALL, ANLL, CML, and CGL) are defined in Table 2.5; CMMOL = chronic myelomonocytic leukemia.

Table 2.7

Calculated Median Lethal Dose D_{50} for Man Vs. Dose Rate to the Bone Marrow for Marrow-Syndrome Mode for Uniform Exposure to Low-LET Radiation: Minimal Treatment Category

Exposure Category	Dose Rate (Gy/hr)	Median Lethal Dose			Shape Parameter[c]			Threshold[d]		
		D_{50} (Gy)[a]	L[b]	U[b]	Central	L	U	Central	L	U
Brief[e]	≥10	3.0	2.5	3.5	6	4	8	1.5	1.2	1.8
Brief	1	3.1	2.5	3.7	6	4	8	1.6	1.3	1.9
Brief	0.1	3.7	3.1	4.3	6	4	8	1.9	1.6	2.2
Protracted[e]	0.05	4.4	3.6	5.2	6	4	8	2.2	1.8	2.6
Protracted	0.01	10	8	12	6	4	8	5.0	4.0	6.0

[a]Based on dose rate model (Scott et al., 1988a) with high dose rate anchor of 3 Gy, and recovery parameter θ_1 of 0.072 Gy^2/hr based on Mexican family (Lushbaugh, 1972) exposed in their home to ^{60}CO gammas and Japanese fishermen (Kumatori, 1971; 1980) exposed to fallout radiation. Values rounded to nearest tenth to illustrate dose rate dependence of model. Results presumed to be accurate only to the nearest 0.5 Gy. Upper and lower bounds on θ_1 based on an exploratory analysis of the data are 0.084 and 0.06 Gy^2/hr. These bounds do not reflect uncertainties in the dosimetry for the Mexican family or the Japanese fisherman.

[b]Symmetric upper and lower bounds were constructed based on upper and lower bounds on θ_∞ of 3.5 Gy and 2.5 Gy, respectively (Young et al., 1987), and the bounds on θ_1 given in footnote a.

[c]Based on the ratio LD_{90}/LD_{10} extrapolated from animal data to a 70 kg mammal (Morris and Jones, 1988b) and Weibull model (Scott et al., 1988a).

[d]Based on large body of animal data obtained at different dose rates and for different radiation qualities (Jones, 1981). No deaths were observed at doses below about 50 percent of the median lethal dose.

[e]Brief implies dose rates equal to or greater than 0.06 Gy/hr. Dose rates below this range are considered protracted exposure.

Table 2.8

Calculated Median Lethal Dose D_{50} for Man Vs. Dose Rate to the Bone Marrow for Marrow-Syndrome Mode for Uniform Exposure to Low-LET Radiation: Supportive Treatment Category

Exposure Category	Dose Rate (Gy/hr)	Median Lethal Dose			Shape Parameter[c]			Threshold[d]		
		D_{50} (Gy)[a]	L[b]	U[b]	Central	L	U	Central	L	U
Brief[e]	≥10	4.5	3.7	5.3	6	4	8	2.3	1.9	2.7
Brief	1	4.7	3.8	5.6	6	4	8	2.4	1.9	2.9
Brief	0.1	5.6	4.7	6.5	6	4	8	2.8	2.3	3.3
Protracted[e]	0.05	6.6	5.4	7.8	6	4	8	3.3	2.7	3.9
Protracted	0.01	15	12	18	6	4	8	7.5	6.0	9.0

[a]Based on protection factor of about 1.5 derived from animal data (MacVittie et al., 1984; Perman et al., 1962; Sorensen et al., 1960). Values rounded to nearest tenth to illustrate dose rate dependence of model. Results presumed to be accurate only to the nearest 0.5 Gy.

[b]Also based on a protection factor of 1.5 provided by supportive treatment.

[c]Central estimate, lower bound, U; upper bound, L; based on animal data assuming no influence of medical treatment on shape parameter. Same values as in Table 2.7.

[d]See footnote d in Table 2.7.

[e]Brief implies dose rates equal to or greater than 0.06 Gy/hr. Dose rates below this range are considered protracted exposure.

Table 2.9

Relationship Between Total-Body Dose and Survival Time for Brief or Protracted Total-Body Exposure (Assuming only minimal treatment)

Type of Exposure	Dose Range (Gy)	Likely Time to Death (Days)
Brief	>2[a]	<60
Brief	<2[b]	Death from early effects unlikely
Protracted[c]	>8[d]	42-179
Protracted	<4[e]	Death from early effects unlikely

[a]Based on atomic bomb victims (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, 1956). None died from early effects even though only bed rest was used as treatment while in the hospital.

[c]Brief refers to dose rates greater than or equal to 0.06 Gy/hr. Dose rates less than 0.06 Gy/hr are considered protracted exposure.

[d]Based on Mexican family exposed to ^{60}Co in their home (Lushbaugh, 1974).

[e]Based on 23 Japanese fishermen exposed to the same radioactive cloud as the Marshall Islanders (Kumatori et al., 1980).

Table 2.10

Survival Time of Victims of the Chernobyl Nuclear Accident That Were Treated at the Specialized Station Hospital[a]

Degree of Severity	Number of Patients	Dose to Bone Marrow (Gy)	Deaths From Acute Radiation Syndrome	Survival Times (days)
First Degree Slight	31	0.8-2.1	--	--
Second Degree Moderate	43	2.0-4.0	1	96
Third Degree Severe	21	4.2-6.3	7	16,18,21,23, 32,34,48
Fourth Degree Extremely Severe	20	6-16	19[b]	14,14,14,15 17,17,18,18, 18,20,21,23 24,24,25,30, 48,86,91
Total	115		27[c]	

[a]From Gus'kova (1987).

[b]One other patient with fourth degree severity died in Kiev on the 10th day from combined thermal and radiation injuries.

[c]In addition to those who died from the acute radiation syndrome, one person was pronounced dead at the workplace because he was never found and one died during the first 12 hours in the station hospital in Pripyat' from thermal burns.

there may be five times that total today that could be used for intensive treatment. Unfortunately, these facilities have many ill patients and empty beds are rare. No study directed specifically to determining the availability of definitive care centers willing and able to deal effectively with victims of radiation accidents appears to have been carried out. In view of this, and the limited efficacy of bone marrow transplantation under the conditions present at Chernobyl, we have not developed a model appropriate for intensive treatment.

2.2.4 Gastrointestinal Tract

2.2.4.1 Nature of Effects

Irradiation of the abdomen by external radiation or by ingested radionuclides may lead to both the prodromal syndrome and gastrointestinal deaths. The prodromal syndrome was previously discussed.

Intestinal radiation deaths have been reported in experimental animals given lethal external radiation doses in the range 10 to 50 Gy (Bond et al., 1965). This mode of death was initially described in irradiated mice that died between 3 to 5 days. In large mammalian species, the mean survival time varies between 3.5 and 9 days (Bond et al., 1965). Deaths in man occurring within 9 days after accidental exposure have been rare. One criticality accident victim died 9 days after the accident from necrosis of his entire small intestine (Hempelman et al., 1952).

The sequence of post-irradiation effects in the intestine relate to the total-body radiation dose (Young, 1987). At doses between 3 to 8 Gy, temporary injury to epithelial cell junctions in the intestinal lining may permit the escape of endotoxins into the blood. For doses of 7-10 Gy, septicemia is an important cause of death and is related to injury to the bone marrow as well as the intestine. At doses just above 10 Gy, death is usually the result of three lesions: essentially complete bone marrow stem cell destruction, immuno-incompetence, and septico-toxemia. At higher doses, serum electrolye imbalance plays an increasingly important role. These conditions develop within a few days and lead to symptoms of cramping, abdominal pain and diarrhea, followed by shock and death.

The physiological mechanisms that have been most often proposed as the primary ones leading to intestinal radiation death are fluid and electrolyte loss (Quastler, 1956; Jackson et al., 1958; Jackson and Enternman, 1958; Caster and Armstrong, 1956), action of bile salts on the damaged intestinal mucosa (Jackson and Geraci, 1986; Sullivan, 1962; Sullivan, 1965; Sullivan et al., 1965) bacterial toxemia (Taketa, 1962; Carroll and Kimeldorf, 1967), and alterations in the vascular system (Kabal et al., 1972; Watters and Gerber, 1975a, 1975b; Timmermans and Gerber, 1980).

Whether loss of fluid and electrolyte via the intestinal tract is a primary mechanism of intestinal radiation death is still in question. Results of a recent study in rats exposed to neutrons or gamma rays

(Jackson and Geraci, 1986) indicate that the inability of denuded mucosa of the irradiated small intestine to absorb fluid and electroytes, resulting in hypovolemic shock, was the major mechanism for intestinal radiation death. The conclusion was based on the observation that breakdown and recovery of the intestinal mucosa, as measured by plasma diamine oxidase activity, was directly correlated with changes in plasma volume and extracellular fluid space in lethally irradiated animals. This was further substantiated by the finding that injection of fluid and electrolytes into the intestinal lumen had no effect on survival time, whereas, injection of the same amount of fluid into the peritoneal cavity (where it is rapidly absorbed by the vascular system) significantly prolonged survival of supralethally irradiated animals. In some animals, who also received antibiotic treatment, sufficient mucosal regeneration occurred to prevent intestinal radiation death. However, the animals died from hematopoietic injury and/or lung and kidney damage (Jackson and Geraci, 1986).

The gastrointestinal syndrome among victims of the Chernobyl accident was described by Gus'kova (1987). Ten patients at the Specialized Station Hospital developed diarrhea during the fourth to the eighth day after exposure. Their dose was estimated to be 10 Gy or more. All died within three weeks after irradiation. The occurrence of diarrhea after the eighth day in seven patients was taken to indicate less severe damage than for those who had episodes in the fourth to the eighth day. Because of the water, electrolyte, and protein (supportive treatment) administered, radiation enteritis, which was observed from the 10th to the 25th day was judged not to be the principal cause of death.

2.2.4.2 Dose-Effect Relationships

Results of bone marrow transplantation studies of Thomas et al. (1975) indicate that, when sufficient therapy is provided to compensate for hematologic complications, the human total-body dose for intestinal death is above 10 Gy. However, no reliable data based on exposure of humans are available for use in developing a dose-effect relationship for mortality caused by injury to the intestine. Data based on exposure of laboratory animals were used to arrive at dose-effect relationships. Because different mammals respond in a similar way to irradiation of the gastrointestinal tract, this is a reasonable approach (Bond et al., 1965; Maisin et al., 1971). Parameters for estimating mortality risks are summarized in Table 2.11. The resulting dose-effect relationships are plotted in Figure 2.5. The information on which they are based is discussed below.

For brief (high dose rate) 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 along with a shape parameter of 10 and a judgmental threshold of 8 Gy. This estimate of the D_{50} is consistent with the results of the bone marrow transplantation studies of

Table 2.11

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

Parameter	Brief Exposure	Protracted Exposure
D_{50} (Gy)	15[b]	35[c]
Lower Bound	10	25
Upper Bound	20	50
Threshold (Gy)	8[d]	18
Shape Parameter	10[b]	10[b]

[a]Estimates were derived from model calculations based upon limited observations. Brief exposure corresponds to dose rate greater than or equal to 0.06 Gy/hr. Protracted exposure corresponds to dose rates of less than 0.06 Gy/hr. Bound factors for protracted exposure were assumed to be the same as for brief exposure.

[b]Based on exposure of exteriorized rat intestines (Sullivan et al., 1959). The bone marrow transplantation studies of Thomas et al. (1975) indicated that 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; Cross et al., 1978).

[d]Threshold dose assumed to be 1/2 the D_{50} based on best judgment of working group. Values were rounded to nearest Gy.

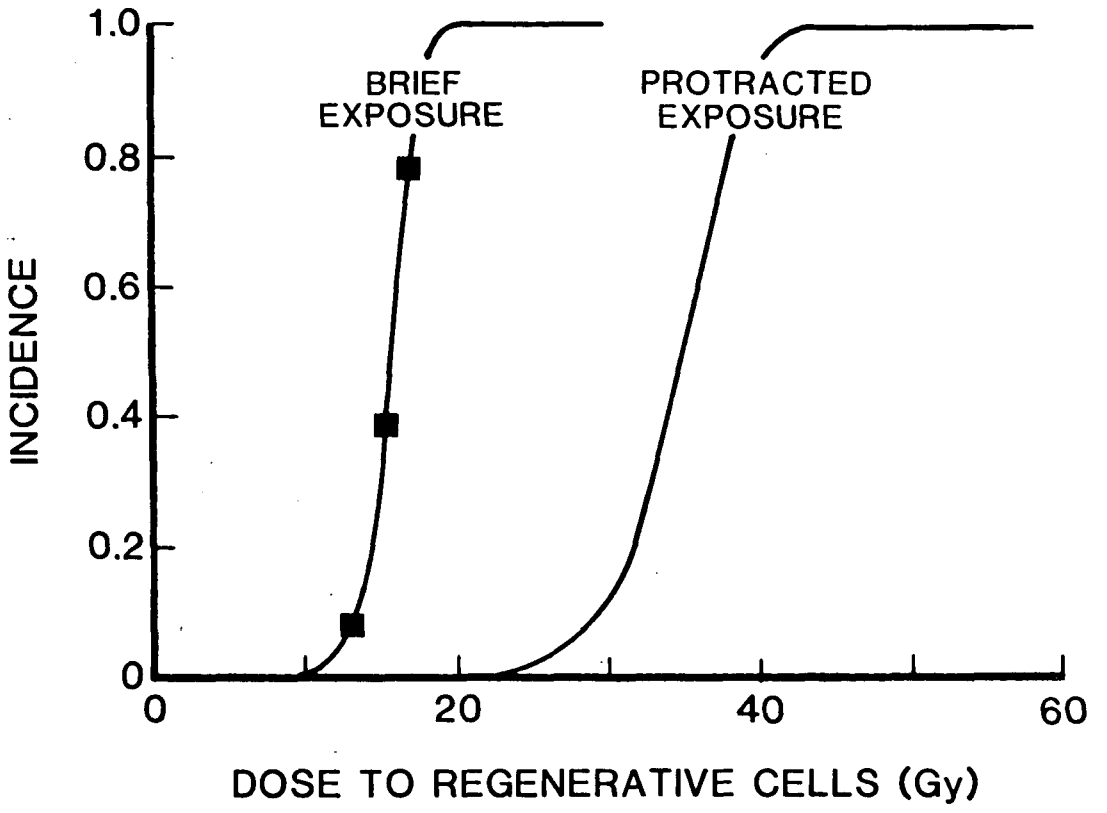

Figure 2.5. Dose-Effect Relationships for the Incidence of Lethality Caused by Injury to the Gastrointestinal Tract. The curve for brief exposure is based on data from Sullivan et al. (1959) for exposure of exteriorized intestine of rats. The curve for protracted beta exposure is based on rats exposed to internal beta radiation from ^{106}Ru-^{106}Rh (Sullivan et al., 1978). A conversion factor of 35 Gy per 330 M Bq/kg was used to obtain the dose to regenerative cells.

Thomas et al. (1975) and with clinical observations from the Chernobyl accident (Gus'kova, 1987; Young, 1988).

For protracted exposure from ingested beta-emitting radionuclides, a median lethal dose of 35 Gy to critical cells in the colon was previously derived for man, based on internal beta irradiation of rats (Cross et al., 1978; WASH 1400, 1975). The dose-effect curve is assumed to have the same shape (V = 10) as was observed for brief exposure. The colon is considered to be a critical component of the gastrointestinal tract for internal radionuclide exposure, because the radioactive contaminant remains in the colon longer than in other parts of the gastrointestinal tract (Sullivan et al., 1978).

Evidence from studies with laboratory animals indicate that age at exposure is also important. 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 M Bq/kg, respectively (Sullivan et al., 1978). These results suggest that the D_{50} for lethality could vary by a factor of 10 with age. However, in neonatal animals radionuclides enter the epithelial cells (Inaba and Lengemann, 1972; Marz and Eisele, 1977; Sullivan et al., 1978) and may lead to greater absorbed doses in neonates than in adults. It is unclear whether the observed age effect is due to increased sensitivity or increased uptake. If possible, some special considerations should be given to the dosimetry problem with neonates. Information provided in Table 2.12 can be used to evaluate life-shortening effects caused by irradiation of the gastrointestinal tract.

2.2.5 Lung

2.2.5.1 Nature of Effects

Early effects of irradiation could be induced in the lung with large radiation doses following a nuclear power plant accident. Irradiation may be the result of total-body external exposure or internal exposure from an inhaled radionuclide. Pulmonary injury and deaths may occur if sufficiently large amounts of radionuclides are inhaled. Because of the large radiation doses required, no early fatalities from pulmonary injury would be expected after uniform total-body irradiation, except where medical treatment for injury to the hematopoietic and gastrointestinal systems is given successfully.

Following the nuclear plant accident at Chernobyl, acute radiation pneumonitis was observed in seven men (Gus'kova, 1987). Respiratory failure occurred within 3 days, followed by death from marked interstitial edema. In general, interstitial pneumonitis developed a few days before death in combination with extremely severe skin burns and intestinal lesions. Death occurred 14 to 30 days after irradiation. Secondary viral infection was a complicating factor. These men also suffered from smoke inhalation, which is known to cause pneumonitis after causing

Table 2.12

Relationships Between Dose to 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]	0-14[b]
Protracted	35[c]	<180[d]

[a]Based on exteriorized exposure of rat intestines (Sullivan et al., 1959). Brief corresponds to dose rates greater than or equal to 0.06 Gy/hr.

[b]Based on atomic bomb victims (UNSCEAR, 1982; Okita, 1975).

[c]Based on rats receiving intragastric (i.e., directly into the stomach) exposure to ^{106}Ru-^{106}Rh (Sullivan et al., 1978). Protracted corresponds to dose rates less than 0.06 Gy/hr.

[d]Based on dogs receiving intragastric exposure to ^{106}Ru-^{106}Rh (Sullivan et al., 1978).

pulmonary edema. Whether interactions between thermal, chemical and radiation damage occurred is unknown.

Pulmonary effects from external thoracic irradiation were first reported in 1898 in patients treated for tuberculosis (Bergonie and Teissier, 1898). Radiation pneumonitis was first described in 1922 in patients treated for breast cancer (Groover et al., 1922). The clinical features (Tyler and Blackman, 1922), pathology (Hines, 1922), and physiology (Leach et al., 1942) of radiation pneumonitis have been described in patients undergoing some form of radiotherapy.

Since the advent of large therapeutic exposure fields (whole-body irradiation, upper half-body irradiation, or mantle irradiation) and the use of large, single or fractionated radiation doses in the treatment of neoplastic diseases and aplastic anemias, with or without bone marrow transplantation, it has been evident that a major treatment limitation is pulmonary damage.

Rubin and Casarett (1968) reviewed the earlier reports of pulmonary damage which began with the use of higher energy therapy machines in the 1920s. Gross (1977) and Bortin (1983) reviewed the literature. These reviews point out that radiation is frequently used in combination with other cytotoxic or immunosuppressive drugs or chemicals which can also damage the lung. Although interstitial pneumonitis is a frequent sequela of these combined therapies, it is difficult to develop a simple relationship between radiation dose and pulmonary response.

A lower dose limit for the observation of interstitial pneumonitis can be estimated from these data. The lowest dose in a total-body irradiated patient that was observed to be associated with interstitial pneumonitis was 4 Gy. One out of eleven patients irradiated at 4 Gy developed interstitial pneumonitis (Keane et al., 1981). Three of twenty-seven patients receiving doses from 4 to 6.2 Gy developed interstitial pneumonitis.

The existence of subgroups of the population that may be more sensitive to the development of radiation pneumonitis is an important consideration. Factors that have been suggested to contribute to sensitivity are underlying infection, atherosclerosis, age at exposure (Gross, 1977) and immunosuppression (e.g., related to leukemia or to chemotherapy). Early data (McKintosh and Spritz, 1939), based on radiation therapy without cytotoxic or immunosuppressive drugs, tend to discount the importance of age. Rubin and Casarett (1968) state that "the age of the patient is not an important factor in irradiation of the lung as in other tissue. However, the lung tissue of children is likely to respond more and also recover better than that of adults following similar doses."

More recent information on the importance of age at exposure comes from patients treated with total-body irradiation and bone marrow transplantation. Many were also treated with immunosuppressive and cytotoxic drugs.

One analysis (Weiner et al., 1986) illustrated a two-fold increase in the incidence of interstitial pneumonitis in patients over 21 years of age as compared to younger ages. This finding was consistent with an earlier publication (Meyers et al., 1982) that showed an increase in the relative risk for interstitial pneumonia with increasing age.

Studies with laboratory animals have helped to clarify the dose-response relationship for thoracic irradiation and document the influence of total radiation dose (Collis and Steel, 1982; Phillips and Margolis, 1972; Cardozo et al., 1985), dose rate (Travis et al., 1983; Depledge and Barrett, 1982), and dose fractionation (van Rongen et al., 1986).

Inhaled radionuclides in sufficient quantities will cause radiation pneumonitis in rats and dogs (Filipy et al., 1988; Scott et al., 1987; McClellan et al., 1982). Such an effect has also been reported in a radium plant work that worked in high concentrations of radon gas and radon progeny (Rajewsky, 1939).

Most information on the effects of inhaled radionuclides comes from studies in laboratory animals. The pulmonary lesions are generally similar to those seen with animals exposed to thoracic irradiation (Slauson et al., 1976, 1977). The time course for development of lesions is more delayed than after a brief external irradiation.

Typically, most radiation doses from internal emitters in the lung are delivered at well under 0.06 Gy/hour and may continue for many days to several years. This protraction allows tremendous doses to accumulate before clinical signs are evident; the onset of disease may not be for several months and death from radiation pneumonitis may occur as long as 15 months after inhalation of beta-emitting radionuclides (Scott et al., 1987).

2.2.5.2 Dose-Effect Relationships

2.2.5.2.1 Brief Exposure

Some clinical data are available on the effects of brief photon irradiation of human lungs. Effects of a brief single exposure can also be extrapolated from data for fractionated exposure. With a standard procedure and 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. The single dose arrived at in this way is called the nominal standard dose (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 tolerance to be 9 Gy (900 ret) for 5 percent incidence of radiation pneumonitis and 10.4 Gy (1040 ret) for 50 percent incidence. A total lung dose of 7 Gy (700 ret) should cause no measurable changes (UNSCEAR, 1982).

Van Dyk et al. (1981) provide dose-effect information for lethality from radiation pneumonitis in humans after brief single exposure to external photon radiation delivered at high dose rates to the upper body. The data along with other related data are presented in Table 2.13. Van Dyk et al. (1981) fitted the data with a probit model and arrived at an estimate of 9.3 Gy for the D_{50}.

Data based on exposure of laboratory animals were used to determine the shape of the dose-effect curve. As shown in Figure 2.6, the data are consistent with a judgmental threshold dose of X = 0.5, i.e., 50 percent of the median lethal dose. It is shown in Figure 2.7 that the curve in Figure 2.6, derived from animal data, adequately predicts data for man.

Parameters derived for the dose-effect relationships for man are given in Table 2.14. Parameter estimates in Table 2.14 are based on adaptation of the Dose Rate Model discussed in Section 2.2.3.3 with the parameter estimate for Θ_1 for lung obtained from data for internal beta irradiation of the lung of dogs (McClellan et al., 1982) and X-ray irradiation of the thorax of rats (Cordozo et al., 1985). The parameter Θ_∞ was fixed at 10 Gy based on data for man (Van Dyk et al., 1981; Mah et al., 1987; Phillips and Margolis, 1972). Estimates obtained for the Dose Rate Model parameter Θ_1 are given in Table 2.15.

2.2.5.2.2 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 plant worker (Rajewsky, 1939). Data for lethality in dogs (McClellan et al., 1982) after inhalation exposure to insoluble beta-emitting aerosols have therefore been used to develop Dose Rate Model parameter estimates for humans. Beagle dogs were exposed by inhalation to ^{90}Y, ^{91}Y or ^{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. Dose-response curves for death from radiation pneumonitis are shown in Figure 2.8. Also shown are data for brief upper-body exposure of rats.

2.2.5.2.3 Respiratory-Functional Morbidity

Respiratory-functional morbidity has been defined as having combinations of any three of the following radiation-induced effects in the lung (Scott et al., 1987; Filipy et al., 1988; Filipy et al., 1989): (1) a reduced volume, (2) an increased stiffness, (3) a nonuniform gas distribution, or (4) a reduced alveolar-capillary gas exchange efficiency. For high-energy beta emitters, the D_{50} for respiratory-functional morbidity among rats exposed via inhalation of radioactive aerosols was found to be about the same as for lethality from radiation pneumonitis. However, low

Table 2.13

Estimates of the Risk for Interstitial Pneumonitis as a Function of Photon Radiation Dose[a]

Dose (Gy)	Number of Patients	Number of Cases	Risk %[b]	References
<5.7	65	--	2.0	Van Dyk et al., 1981
5.8-6.2	4	0	0.0	Van Dyk et al., 1981
<6.0[c]	49	1	2.7	Fryer et al., 1978
6.0[c]	24	3	17.5	Fryer et al., 1978
6.0[c]	17	4	27.2	Pino et al., 1982
6.3-6.7	15	--	11.0	Van Dyk et al., 1981
6.8-7.2	26	--	13.0	Van Dyk et al., 1981
7.0	4	4	100.0	Fryer et al., 1978
7.3-7.7	8	--	13.0	Van Dyk et al., 1981
7.8-8.2	10	--	37.0	Van Dyk et al., 1981
8.0	149	28	35.6	Fryer et al., 1978

[a]Unpublished literature review by Dr. Albert A. Spritzer (1987). Some of the same data were used by Fryer et al. (1978) and by Van Dyk et al. (1981). References which contained other relevant data on interstitial pneumonitis were: Weiner et al., 1986; Keane et al., 1981; Meyers et al., 1982; Bortin et al., 1983; Van Bekkum and Lowenberg, 1985; Barrett et al., 1982; Ognibene et al., 1986; Meyers et al., 1983; Winston et al., 1983; Bortin, 1983; Ringden et al., 1983; Goolden et al., 1983; Thomas et al., 1982; Thames et al., 1982; Mah et al., 1987; Bortin and Rimm, 1982; Salazar et al., 1978; Depledge et al., 1983; Colin et al., 1985; Jochelso et al., 1986; Kim et al., 1985; Cordier et al., 1984; Dagle and Sanders, 1984; Champlin and Gale, 1984; Charbora et al., 1977; Tefft, 1977; Rosewit and White, 1977; Fajardo and Berthrong, 1981; McKenna et al., 1987; Collis, 1980; Schronagel and McVie, 1983; Muggia et al., 1983; Catane et al., 1979; Van Dyk et al., 1980; Cohen and Creditor, 1989; Van Dyk, 1983; Wara et al., 1973; Gross, 1977; Jennings, 1962; Chang et al., 1986; Kinsella et al., 1982; Appelbaum et al., 1982.

[b]Based on actuarial analysis.

[c]Data for different doses or from different studies were not combined at this dose level. Note that doses at this level overlap those for the 5.8-6.2 Gy group.

Table 2.13

Estimates of the Risk for Interstitial Pneumonitis as a Function of Photon Radiation Dose[a] (Concluded)

Dose (Gy)	Number of Patients	Number of Cases	Risk %[b]	References
8.0	5	4	84.0	Pino et al., 1982
8.3-8.7	23	--	41.0	Van Dyk et al., 1981
8.8-9.2	93	--	28.0	Van Dyk et al., 1981
9.3-9.7	32	--	49.0	Van Dyk et al., 1981
10.0	23	12	83.5	Fryer et al., 1978
10.0	8	5	80.5	Pino et al., 1982
10.3-10.7	2	--	100.0	Van Dyk et al., 1981
10.8-11.2	7	--	100.0	Van Dyk et al., 1981
11.3-11.7	13	--	74.0	Van Dyk et al., 1981
11.8-12.2	5	--	80.0	Van Dyk et al., 1981

[a]Unpublished literature review by Dr. Albert A. Spritzer (1987). Some of the same data were used by Fryer et al. (1978) and by Van Dyk et al. (1981). References which contained other relevant data on interstitial pneumonitis were: Weiner et al., 1986; Keane et al., 1981; Meyers et al., 1982; Bortin et al., 1983; Van Bekkum and Lowenberg, 1985; Barrett et al., 1982; Ognibene et al., 1986; Meyers et al., 1983; Winston et al., 1983; Bortin, 1983; Ringden et al., 1983; Goolden et al., 1983; Thomas et al., 1982; Thames et al., 1982; Mah et al., 1987; Bortin and Rimm, 1982; Salazar et al., 1978; Depledge et al., 1983; Colin et al., 1985; Jochelso et al., 1986; Kim et al., 1985; Cordier et al., 1984; Dagle and Sanders, 1984; Champlin and Gale, 1984; Charbora et al., 1977; Tefft, 1977; Rosewit and White, 1977; Fajardo and Berthrong, 1981; McKenna et al., 1987; Collis, 1980; Schronagel and McVie, 1983; Muggia et al., 1983; Catane et al., 1979; Van Dyk et al., 1980; Cohen and Creditor, 1989; Van Dyk, 1983; Wara et al., 1973; Gross, 1977; Jennings, 1962; Chang et al., 1986; Kinsella et al., 1982; Appelbaum et al., 1982.

[b]Based on actuarial analysis.

[c]Data for different doses or from different studies were not combined at this dose level. Note that doses at this level overlap those for the 5.8-6.2 Gy group.

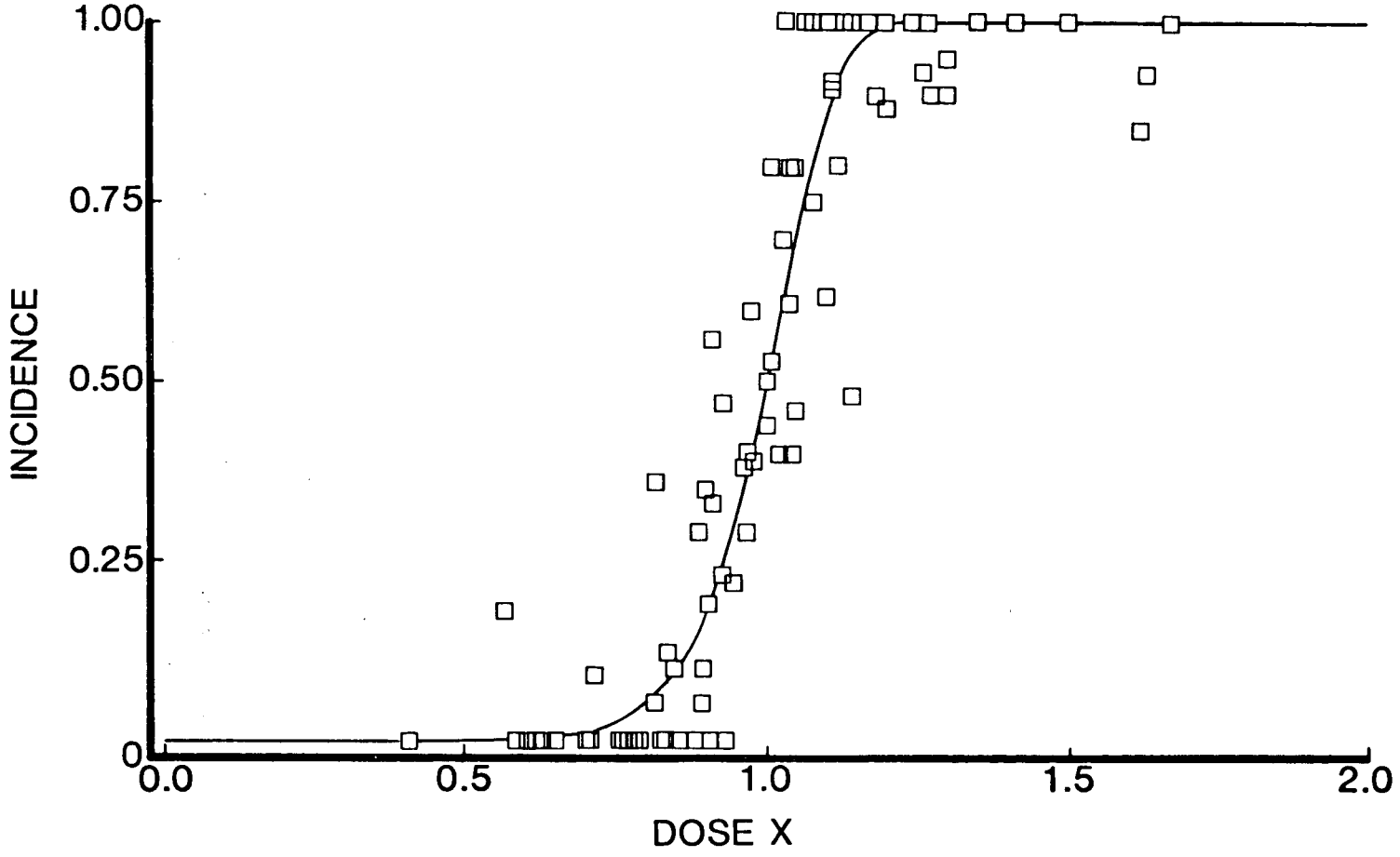

Figure 2.6. Dose-Effect Relationship for the Incidence of Acute Lethality From Pulmonary Injury After Single, Thoracic (Photon) Irradiation of Mice and Rats Based on 160-210 Day Lethality (Cardozo et al., 1985; Hill, 1983; Travis and De Luca, 1985; Miller et al., 1986; Collis and Steel, 1982; Kurohara and Casarett, 1972; Siemann et al., 1982; Ward et al., 1982; Dunjic et al., 1960; Phillips and Margolis, 1972; Travis and Down, 1981). Use of the normalized dose X in D_{50} units eliminated much of the variability associated with unit of dose, strain, species, and radiation dose rate. Use of these data with the Weibull model leads to a shape parameter estimate of approximately 12 (11.6 ± 1.2 rounded). The smooth curve is based on the Weibull model. The zeros on both axes are offset. The figure was obtained from another publication (Scott et al., 1989)

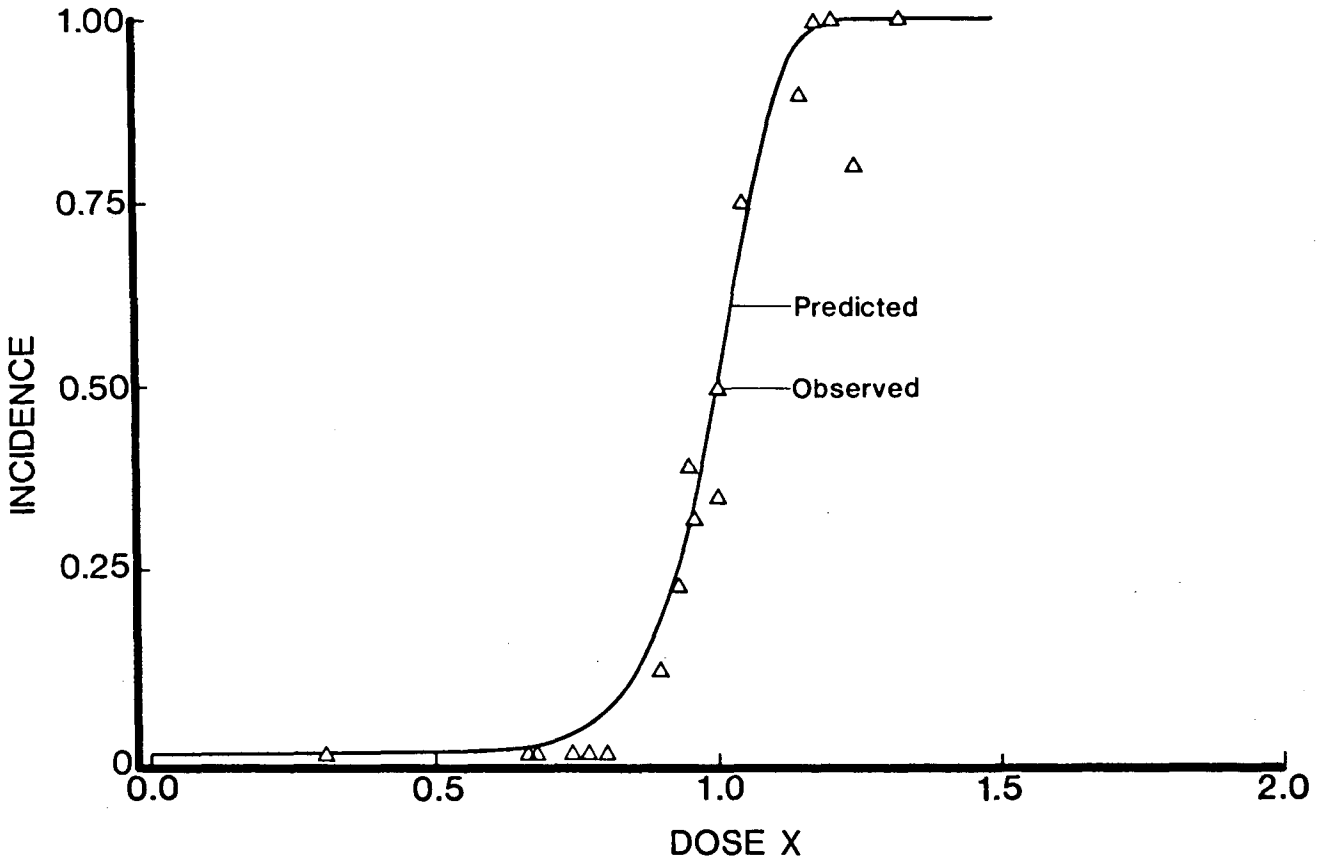

Figure 2.7. Dose-Effect Relationship for the Incidence of Radiation Pneumonitis in Man After Single, Thoracic (Photon) Irradiation, or After a Fractionated Irradiation With Calculation of the Equivalent Dose Administered in a Single Exposure. Use of normalized dose X in dimensionless D_{50} units eliminated much of the variability in the dose-effect relationship due to differences in dose unit (e.g., ret, estimated single dose ED, Gy). A shape parameter of 12 was used for the Weibull model based on the animal data in Figure 2.6, to obtain the smooth curve. The predictions are consistent with the data for man. Sources of the data (Van Dyk et al., 1981; Prato et al., 1977; Mah et al., 1987; Phillips and Margolis, 1972). The zeros on both axes are offset. The figure was obtained from another publication (Scott et al., 1989).

Table 2.14

Model Parameters for Lung for Healthy Young Adults (Age 40 or Less) or Children for Pulmonary-Syndrome Lethality Based on Dose Rate Model (Scott et al., 1988a) Adapted for Lung, for External or Internal Low-LET Irradiation or Both[a]

Exposure Category	Dose Rate (Gy/hr)	Calculated D_{50} (Gy)			Shape Parameter			Threshold (Gy)[b]		
		Central	Lower	Upper	External[c]	Internal[d]	Both[e]	Central	L	U
Brief[g]	≥100	10	8	12	12(9-14)	NA[f]	NA[f]	5	4	6
Brief	10	15	10	20	12(9-14)	NA	NA	7	5	9
Brief	1	40	20	60	12(9-14)	NA	NA	20	10	30
Brief	0.5	70	40	100	12(9-14)	NA	NA	40	20	60
Brief	0.1	310	160	460	12(9-14)	5(4-6)	7(5-12)	160	80	230
Protracted[g]	0.05	610	310	910	12(9-14)	5(4-6)	7(5-12)	310	160	460

[a]With dose rate model (Scott et al., 1988a) the D_{50} (Gy) = θ_1/(dose rate) + θ_∞ where from Table 2.15 θ_1 = 30 Gy^2/hr with upper and lower bounds of 15 and 45 Gy^2/hr, and θ_∞ = 10 Gy with upper and lower bounds of 8 and 12 Gy. The high dose rate anchor θ_∞ = 10 Gy for the central estimate is based on the incidence of radiation pneumonitis in man (Van Dyk et al., 1981; Mah et al., 1987; Phillips and Margolis, 1972) after thoracic irradiation at high dose rates. Doses greater than 20 Gy rounded to nearest 10 Gy.

[b]Based on judgments of Working Group that the threshold dose is a factor of about 2 below the D_{50}; L and U represent judgmental lower and upper bounds on the threshold which were assumed to be symmetric.

[c]Based on thoracic X- or gamma-irradiation of mice and rats at high or moderate dose rates (Cardozo et al., 1985; Hill, 1983; Travis and De Luca, 1985; Miller et al., 1986; Collis and Steel, 1982; Kurohara and Casarett, 1972; Siemann et al., 1982; Ward et al., 1982; Dunjic et al., 1960; Phillips and Margolis, 1972; Travis and Down, 1981). Data for 160 to 180 day mortality were used. Lower and upper bounds given within parentheses based on asymptotic 95% confidence interval obtained using SAS software (SAS, 1985).

[d]Based on rats exposed via inhalation to beta-emitting radionuclides at the Inhalation Toxicology Research Institute (Scott et al., 1987b) or at Battelle Pacific Northwest Laboratory (Filipy et al., 1989). Lower and upper bounds given within parentheses based on data for death only from radiation pneumonitis and pulmonary fibrosis within 1.5 years after inhalation exposure.

[e]Judgmental central estimate, lower and upper bounds based on assumption that significant internal and external doses are both delivered so that lower bound is same as central estimate for internal only and upper bound is central estimate for external only. When most of the dose is due to either internal or external radiation, these bounds should not be used.

[f]NA refers to not applicable to internal irradiation. For dose rates in the ranges listed for brief, exposure parameter estimates for external radiation can be used.

[g]Brief implies dose rates equal to or greater than 0.06 Gy/hr. Protracted implies dose rates below this range.

Table 2.15

Estimates of Dose-Rate Model Parameter Θ_1 for Pulmonary Syndrome Mode Lethality

Species	Radiation Type	Parameter Estimate[a] (Gy^2/hr)	Reference
Dog	^{90}Y-Beta	46	McClellan et al., 1982
Dog	^{91}Y-Beta	21	McClellan et al., 1982
Dog	^{144}Ce-Beta	38	McClellan et al., 1982
Dog	^{90}Sr-Beta	21	McClellan et al., 1982
Rat	X-Rays	28	Cordozo et al., 1985
		Average 31 ± 9.8	

[a]Details on parameter estimation are provided elsewhere (Scott et al., 1989). Approximate 90 percentile lower and upper bounds can be taken as 15 and 45 Gy^2/hr based on these data. The parameter Θ_1, when divided by the dose rate, gives the increase in the LD_{50} above that for a prompt exposure which is due to recovery and repair occurring during protracted irradiation.

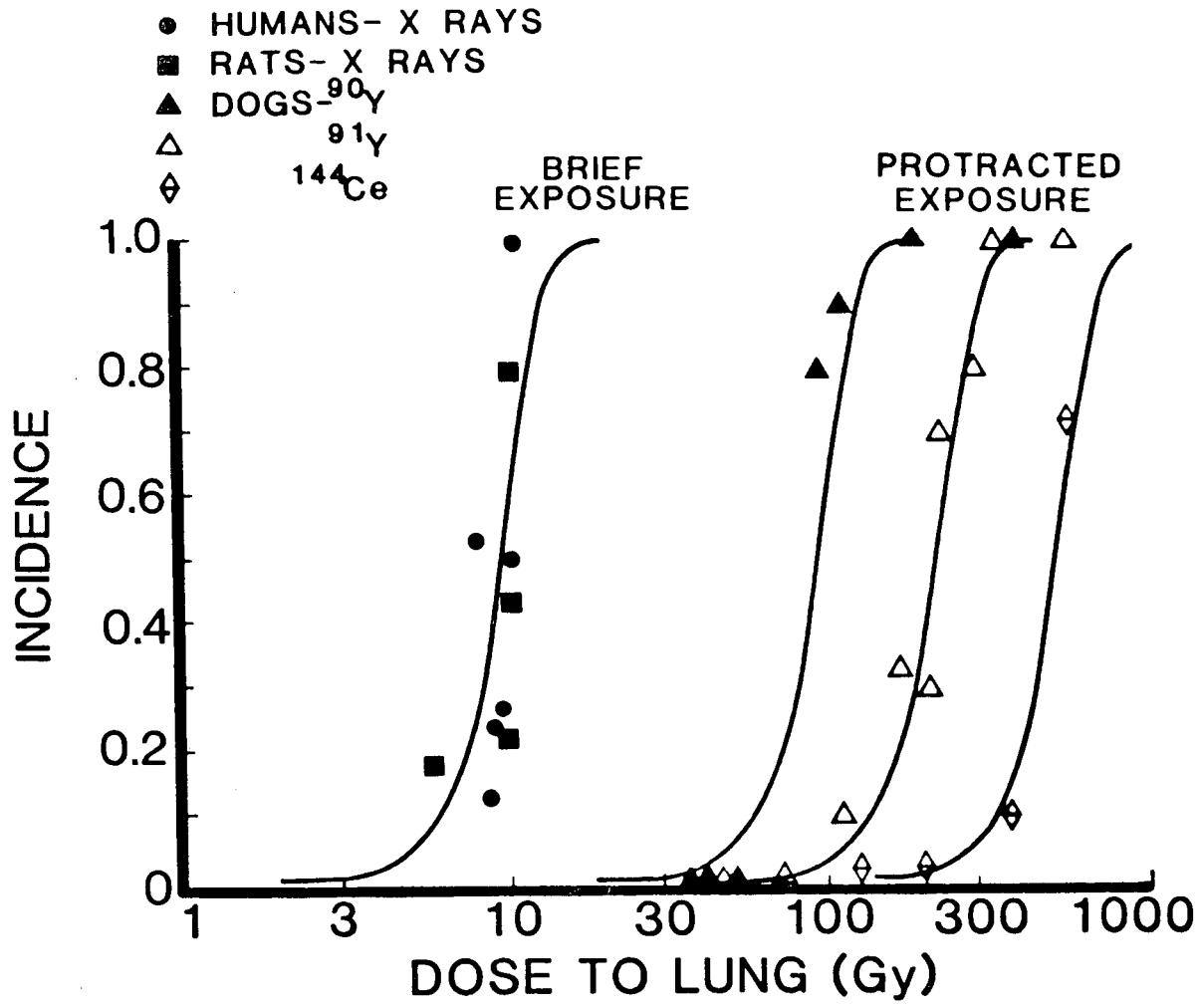

Figure 2.8. Dose-Effect Relationships for the Incidence of Mortality After Irradiation of the Lung. The data for pneumonitis in humans is based on a report by Van Dyk et al. (1981) for exposure of the thorax. Most individuals with pneumonitis died. The data for upper-body exposure of rats are from Dunjic 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. The zero on the vertical axis is offset.

energy beta emissions from ^{147}Pm or alpha emissions from ^{238}Pu appear to require only about 1/4 as much dose to the lung for causing respiratory-functional morbidity as is required for death from radiation pneumonitis (Scott et al., 1988b). Also, use of the same shape parameter (V = 5) for both lethality and morbidity has led to an adequate representation of the data for both high and low energy beta, as well as for alpha irradiation (Scott et al., 1987, 1988b).

Respiratory dysfunction following inhalation of a nonlethal concentration of high energy beta-emitting radionuclides has been demonstrated using pulmonary function measurements in dogs (Mauderly et al., 1973, 1980a, 1980b). Early dysfunctions observed included defects in the distribution of ventilation and alveolar-capillary gas exchange. Dogs measured for respiratory dysfunction after cumulative lung doses of about one-half the median lethal dose were functionally impaired.

2.2.5.2.4 Modifying Factors

Three therapeutic modalities have been advocated for radiation pneumonitis: corticosteroids, antibiotics, and anticoagulants (Gross, 1977). Only corticosterioid treatment has had some success, and then only with acute radiation pneumonitis. The approach generally taken to reduce the incidence of radiation pneumonitis in radiation therapy for cancer is fractionation of the radiation exposure and reduction of the required total radiation dose by combining the radiation treatment with anticancer drugs. For inhaled radionuclides, lung lavage can be used 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 about 50 percent (Muggenberg et al., 1975, 1977). 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, such as lung lavage, 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 aged 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 2.14 should be divided by 2 for aged individuals.

The D_{50} for immature dogs was also about a factor of 2 less than that for young adults (McClellan et al., 1982). However, the dose rate patterns differed for the young adults and the immature, suggesting that the different D_{50}s may be due to differences in dose rate pattern.

2.2.6 Thyroid

2.2.6.1 Nature of Effects

Early and continuing effects associated with irradiation of the thyroid include acute radiation thyroiditis, chronic lymphocytic thyroiditis, and hypothyroidism. A detailed discussion of these effects is given in Appendix A, "Thyroid Effects."

Acute radiation thyroiditis generally occurs within 2 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 (see Appendix A, "Thyroid Effects").

Chronic lymphocytic thyroiditis is an inflammation of the thyroid that occurs years after radiation exposure. The predominance of lymphocytes in the lesion suggests an autoimmune basis. Chronic thyroiditis is usually associated with hypothyroidism or benign thyroid nodules.
Thyroid nodules developed in the Marshallese native children who inhaled radioiodine isotopes (Conrad et al., 1980).

Hypothyroidism is an abnormal metabolic state due to insufficient amounts of thyroid hormone for normal physiologic function. In advanced forms, it can lead to mental slowness, fluid retention, muscle cramps and a generalized decrease in bodily functions. Signs of hypothyroidism may occur years after radiation exposure. In some cases, however, signs may be so mild as to be detected only by biochemical tests. Generally, radiation-induced early effects in the thyroid respond to medical treatment and do not result in death.

2.2.6.2 Dose-Effect Relationships

2.2.6.2.1 Acute Radiation Thyroiditis

Acute radiation thyroiditis has been observed in patients given ^{131}I to ablate the thyroid. A D_{50} of 1200 Gy and a threshold of 200 Gy for protracted exposure was estimated from studies of such patients. In these studies, about a 5 percent increase in risk was associated with each 100 Gy increment in dose. The use of a shape parameter of about 2 in the Weibull model is consistent with this observation.

Clinical radiation thyroiditis after a brief external exposure has only been reported in one case (Hemplemann et al., 1952). Following the second criticality accident at Los Alamos, radiation thyroiditis was diagnosed 10 years later. His hypothyroidism was adequately controlled by thyroxin. About 87 percent of his estimated total body dose of 1.92 Gy was due to

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[a]Unpublished literature review by Dr. Joseph A. Watson (1987).

neutrons (1.66 Gy). The remainder was due to gamma radiation (Hemplemann et al., 1980). If, as Appendix A suggests, brief external exposure to low-LET radiation is five times as effective as chronic ^{131}I exposure, a brief photon dose of more than 40 Gy would be required to induce acute radiation thyroiditis. It is unlikely that an individual would receive an external dose sufficient to cause acute thyroiditis without receiving lethal injury to the bone marrow, gastrointestinal tract, lungs and central nervous system. Therefore, no model was developed for acute radiation thyroiditis for brief external exposure. Model parameters for chronic irradiation are given in Table 2.16.

2.2.6.2.2 Hypothyroidism

Recent literature on the appearance of early-occurring hypothyroidism, as well as subsequent development of late-onset hypothyroidism was reviewed.[a] Six publications present results of more than 6000 patients treated for Grave's and other diseases of the thyroid (Cunnien et al., 1982; Holm et al., 1982; Sridama et al., 1984; Lowdell et al., 1985; Alevizaki et al., 1985; Goolden and Stewart, 1986). The following conclusions were reached:

1. A 10 Gy threshold is indicated in Appendix A. However, none of the studies involved doses below 10 Gy and significant incidences of hypothyroidism were found in all studies.

2. Low-dose, ^{131}I therapy uses amounts of ^{131}I corresponding to radiation doses calculated to be in the 30 Gy to 50 Gy range. The range results from intentional variation in doses according to thyroid size, with the larger glands receiving a larger activity per gram of tissue. These doses resulted in an increased incidence of hypothyroidism (1-year follow-up) in 125 patients of 11.7 percent (Sridama et al., 1984) and in 261 patients of 10 percent (Goolden and Stewart, 1986). In a study where 164 patients were each given 2 mCi of ^{131}I, with no measurement of thyroid size, and with an estimated dose of more than 20 Gy, the 1-year incidence of hypothyroidism was 6 percent (Lowdell et al., 1985).

3. At early times the prevalence of post-therapy hypothyroidism was found to depend strongly on radiation dose (Cunnien et al., 1982; Alevizaki et al., 1985). In a subgroup of 317 patients that received a ^{131}I dose of 200 Gy for diffuse and nodular goiter, 77.5 percent of the group were hypothyroid within 6 months.

4. The prevalence of late-onset hypothyroidism increases with time in all ^{131}I treatment groups. As an example, in patients receiving ^{131}I therapy doses (30 to 50 Gy), the prevalence of permanent hypothyroidism was 11.5 percent in the first year. At

Table 2.16

Median Dose Estimate (D_{50}) and Response Curve Shape Parameter (V) for Acute Radiation Thyroiditis After Thyroid Irradiation[a] from Internally Deposited ^{131}I

Parameter[b]	Estimate
D_{50} (Gy)	1,200
Shape[b]	1.9
Threshold (Gy)	200

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

[b]Shape parameter = $2.6/\ln (D_{50}/D_5)$.

the end of the sixth, ninth and eleventh years, the prevalence was 32.7 percent, 47.3 percent and 72.7 percent, respectively (Sridama et al., 1984). All patient groups followed for long times show similar increases in prevalence (Holm et al., 1982; Alevizaki et al., 1985; Lowdell et al., 1985; Goolden and Stewart, 1986). The prevalence of late-onset hypothyroidism increases by about 3 percent per year to about 15 years (Holm et al., 1982; Alevizaki et al., 1985; Stewart, 1986).

5. Males may be more resistant to hypothyroidism than females (Holm et al., 1982; Alevizaki et al., 1985).

Some recently published data was also reviewed[a] that relate to hypothyroidism after fractionated (therapeutic) partial body exposure of humans to external radiation (Schimpff et al., 1980; Smith et al., 1981; Morgan et al., 1985; Green et al., 1980; Constine et al., 1984; Fleming et al., 1985; Bruning et al., 1985; Joensuu and Viikari, 1986). The age of the patients was generally in the 18 to 35 years range. No relationship was found between incidence of thyroid damage and age. The significant dysfunction that was observed after doses of 40 Gy was predominantly of the biochemical type (i.e., depressed thyroxine) and showed a significant increase with time after irradiation. The hypothesis of no influence of age is supported by other pediatric (therapy patient) data for treatment of Hodgkin's and other cancers (Green et al., 1980; Constine et al., 1984; Fleming et al., 1985).

Thyroid dysfunction has also been found in long-term survivors of bone marrow transplantation (Sklar et al., 1982). The estimated dose to the thyroid was about 8 Gy. Thyroid dysfunction occurred in 10 of 23 irradiated patients with a median time of occurrence of 13 months.

The dose-response relationship used for hypothyroidism is identical to the one discussed in Appendix A. The dose-response relationship for estimating the lifetime risk for chronic low-LET irradiation is linear (above a threshold) with 16.7 cases expected for each 10,000 Gy increase in the dose (Appendix A). An upper bound estimate for the threshold dose is 10 Gy. Central and lower bound estimates could not be obtained from currently available data. External radiation is expected to be about five times as effective as chronic ^{131}I exposure for a 1-year followup (Appendix A).

2.2.6.2.3 Thyroid Ablation

Thyroid ablation by irradiation can also occur. However, available data are insufficient for development of a dose-effect relationship for thyroid ablation.

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[a]Unpublished literature review by Dr. Joseph A. Watson (1987).

2.2.7 Skin

2.2.7.1 Nature of Effects

Early radiation effects in the skin can be classified as: (1) erythema, (2) transepidermal injury, and (3) dermal necrosis (NRCP Report 42, 1974; Potten, 1985). Erythema is a reddening of the skin equivalent to a first degree thermal burn or sunburn and appears to result from vascular dilation or increased blood flow (Archambeau, 1987; Saenger et al., 1980). Characteristically, it can occur in two or more waves. The first appears within 24 to 48 hours when elicited by a single dose of low-LET radiation of about 15 Gy or more to a 5 cm x 12 cm parasternal field. It fades in several days but recurs later and can last for 1 to 1 1/2 weeks. Dry desquamation, or scaling, usually follows the erythema. The severity of the reaction depends on several factors that include the anatomical location, the vascularity, the genetic background, as well as the age of the individual (Rubin and Casarett, 1968). Definitive medical care is not necessary (Archambeau, 1987).

Transepithelial injury or moist desquamation is equivalent to a second degree thermal burn in which blisters form in the epidermis. Erythema occurs soon after a single low-LET dose of more than 15 to 20 Gy to a relatively large area, followed by blister formation in 1 to 2 weeks. Medical care is often needed for these types of injuries, and usually leads to healing. The new skin, however, is usually pigmented, thin, and easily injured.

Dose and time dependencies can be obtained from radiotherapy data for small field irradiations. Moist desquamation appears in 2 to 3 weeks in one-half of those that receive a dose of about 20 Gy to areas of about 35 to 80 cm^2 (Andrews and Coppedge, 1951; Ellis, 1942; Jolles and Mitchell, 1947; Langham et al., 1967; Paterson, 1963; Archambeau, 1987). The most severe reaction occurs at around 3 weeks. An individual receiving a 20 Gy uniform total-body gamma radiation dose would die from the gastrointestinal syndrome mode before the desquamation reactions occurred.

For photon irradiation of circular fields, the effect of field size can be estimated using the following formula:

$$\text{Dose required} = K_1 \ (\text{area})^{-0.16} = K_2 \ (\text{diameter})^{-0.33}$$

where the area is in cm^2, the diameter is in cm, and K_1 and K_2 are fixed (Cohen, 1966; von Essen, 1968). The model was developed from data for areas less than 400 cm^2. The exponents (-0.16 and -0.33) depend on photon energy and may not be appropriate for very low or very high-energy photons (Cohen, 1966).

Dermal necrosis is a severe injury occurring with doses greater than 20 to 30 Gy in which there is sloughing of the epidermis and widespread cell destruction in the dermis and underlying tissues. The lesions resemble those caused by severe scalding or chemical burns and are followed by intense pain. Medical treatment is required and may involve skin grafting or amputation of an affected limb.

Factors other than area irradiated influence the skin response to ionizing radiation (Langham, 1967; Archambeau, 1987). The severity of the skin response depends on the (1) dose rate and (2) depth-dose distribution.

The depth-dose distribution is of particular importance. Studies on pig skin (which is often selected for study because of its similarity to human skin) show that the dose at about 0.09 mm below the surface is a much better predictor of the potential for transepithelial injury than the surface dose (Mortiz and Henriques, 1952). This depth corresponds roughly to the location of the basal cells of the epidermis, which are regenerative cells, and injury to them is likely to be the biologic basis for epithelial damage.

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 et al., 1984). The beta radiation doses required to produce transepithelial injury in 50 percent of exposed pigs, for 15 to 22.5 mm diameter circular fields, were 30 to 45 Gy for ^{90}Sr, 80 Gy for ^{170}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 (Peel et al., 1984). The median effective dose for transepithelial injury ranged from about 25 Gy for a 40 mm diameter irradiation field to about 450 Gy for a 1 mm diameter field.

Widespread lesions of the skin caused by beta irradiation were observed following the Chernobyl accident (Gus'kova, 1987; Young, 1988). The radiation burns of the skin of firemen and power station staff members were observed in combination with radiation-induced damage to the hematopoietic system. In some cases, doses to the skin may have been 10 to 20 times larger than the dose to the bone marrow. Retention of the radioactive particles in the water-soaked clothes of the firefighters contributed to the high radiation doses to skin.

The evolution of visible lesions was similar to that described by Cronkite (1956), but more severe (Gus'kova, 1987). Primary erythema was observed on the first day, followed by a latent period (3rd to 4th day). In the most severe cases, secondary erythema developed after the 5th to 6th day. First, second, and third degree burns were observed.

2.2.7.2 Dose-Effect Relationships

2.2.7.2.1 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 be used as a basis for deriving limited dose-effect relationships for erythema and transepithelial injury. No information on dermal necrosis is available on which to develop reliable 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. Current literature from 1976 on effects of irradiation of the skin has been reviewed.[a] Results obtained for D_5 and D_{50} estimates are provided in Table 2.17.

Archambeau has recently published a review of the relative radiosensitivity of the skin. Table 2.18 provides a summary based on his paper (Archambeau, 1987).

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

2.2.7.2.2 Erythema

The median dose for erythema and the shape of the dose-effect curve are noted in Table 2.19. The D_{50} of 6 Gy for brief irradiation is based on the data in Table 2.17. The X-ray dose resulting in erythema within 4 weeks in 1/2 of those exposed over a 100 cm^2 area was also previously reported to be about 6 Gy (Langham et al., 1967; Duffy et al., 1934). Model parameters were judged to be applicable to a 0.1 mm depth in the skin and to areas of 50 to 100 cm^2.

2.2.7.2.3 Transepithelial Injury

The effective dose for transepithelial injury and the shape parameter are given in Table 2.19. The D_{50} of 20 Gy for brief irradiation is based on data for 35 to 80 cm^2 areas, as indicated. This estimate is consistent with the value of approximately 25 Gy, based on ^{90}Sr irradiation of 50 cm^2 areas of pig skin (Peel and Hopewell, 1984).

The D_{50} of 80 Gy for protracted irradiation is based on the data in Table 2.17. The shape parameter of 5 was obtained using the equation in Table 2.19 and an estimate of the ratio D_{50}/D_{10} obtained from Langham et al. (1967).

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[a]Unpublished literature review by Dr. Niel Wald (1987).

Table 2.17

Estimates of D_5 and D_{50} for Specific Effects of Irradiation of the Skin[a]

Effect	Exposure	D_5 (Gy)	D_{50} (Gy)
Erythema	Single	3-10[c,d,e,f,g,h,i,j,k,l]	5-7.5[b]
	Fractionated	12-30[g,k,l]	
Dry Desquamation	Single	5-20[c,e,g]	20[b]
	Fractionated	20-50[f,g,k]	34[b]
Moist Desquamation	Single	12-20[c,h]	--
	Fractionated	30-60[f,k]	80[f]
Necrosis	Single	20-30[c,e,g,h]	
	Fractionated	40-60[g,m]	70-100[b,m]

[a]Unpublished literature review by Dr. Niel Wald (1987).
[b]Lushbaugh et al. (1986).
[c]Gongora (1986).
[d]Steive (1986).
[e]Vasilenko (1983).
[f]Fajardo and Berthrong (1981).
[g]Saenger et al. (1980).
[h]Nenot (1985).
[i]Field et al. (1976).
[j]Braun-Falco et al. (1976).
[k]Archambeau (1987).
[l]ICRP 41 (1984).
[m]Upton (1985).

Table 2.18

Time Course of Changes in Skin Related to Increasing Radiation Dose
(Revised from Archambeau, 1987)

Schedule Dose Range Dose Fraction				
Single (Gy)	Multiple (2 Gy/Day)	Gross Change	Onset of Change	Functional Change
3-7	20	Epilation	~18 days	
10-20	20-40	Erythema	12-17 days	Hyperemia
20-30			2-6 days	
10-20	~45	Pigmentation		None
10-20	~45	Dry desquamation	30-70 days	
20-24	45-50	Moist desquamation that heals	30-50 days	Serum leakage; healing regenerates functional barrier
>24	>60	Moist reaction does not heal >50%	30-50 days	Loss of protective barrier
17-24	45-50	Telangiectasia	6 months-years	None
>27	>60	Necrosis nonhealing	Months, years	Loss of protective barrier

Table 2.19

Estimates of Median Dose (D_{50}) and Response-Curve Shape Parameter (V) for Skin Erythema or Transepithelial Injury After Low-LET Irradiation of 50-100 cm^2 Areas

Endpoint	Parameter	Brief Exposure[a]	Protracted Exposure[a]
Erythema	D_{50} (Gy)[b]	6	20
	Lower Bound[e]	5	10
	Upper Bound[e]	7	30
	Shape[d]	5	5
	Lower Bound[e]	4	4
	Upper Bound[e]	6	6
	Threshold[b] (Gy)	3	6[c]
	Lower Bound[e]	2	4[c]
	Upper Bound[e]	4	8[c]
Transepithelial Injury	D_{50} (Gy)	20[f]	80[b]
	Lower Bound[e]	14	60
	Upper Bound[e]	26	100
	Shape[d]	5	5
	Lower Bound[e]	4	4
	Upper Bound[e]	6	6
	Threshold[b]	10	40
	Lower Bound[e]	8	30
	Upper Bound[e]	12	50

[a]Brief exposure indicates dose rates greater than or equal to 0.06 Gy/hr. Protracted exposure indicated dose rates less than 0.06 Gy/hr.

[b]Crude estimate based on data in Table 2.17.

[c]Based on protraction factor of about 2 from D_5 data in Table 2.17.

[d]Calculated with $v = 1.9/\ln (D_{50}/D_{10})$ using dose-response curve provided by Langham et al. (1965) and assumed not to depend on dose rate.

[e]Judgmental values.

[f]Based on data for 35-80 cm^2 area (Andrews and Coppedge, 1951; Ellis, 1942; Jolles and Mitchell, 1947; Langham et al., 1965; Patterson, 1968).

2.2.8 Gonads

2.2.8.1 Effects on the Ovary

The ovary, a relatively radiosensitive organ, contains a fixed number of germ cells. If severely damaged by radiation, these cells cannot be replaced. A detailed review of the effects of radiation and chemotherapy on ovarian function has been published (Damewood and Grochow, 1986). Table 2.20 presents a summary of the findings. No deleterious effects on reproductive function appear after exposure to 0.6 Gy. Doses to the ovary causing temporary suppression of ovulation range from about 1.5 to 5 Gy for brief exposure to low-LET external irradiation. Higher doses are required when the dose is delivered in fractions than for a single exposure. Doses greater than 8 Gy in women under about 40 years of age cause permanent ovulation suppression of ovulation.

Suppression of menstruation is another deleterious effect of irradiation. 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 percent 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 permanent suppression to increase to about 10 to 20 Gy (WASH 1400, 1975).

Peck et al. (1938) carefully analyzed data for permanent suppression of ovulation among 334 patients exposed to photon radiation. Women 40 years or more of age were judged to be more sensitive than those under 40. The data for the under 40 group were used to develop a dose-effect relationship for permanent ovulatory suppression. Parameters for the dose-effect relationship for brief exposure to dose rates greater than or equal to 0.06 Gy/hr are provided in Table 2.21. The model parameters given are based on data for females less than 40 years of age. It was assumed that the majority of child-bearing women would be under 40 years of age. Judgmental upper and lower bounds are provided which should account for errors associated with their use for populations containing a significant proportion of females over 40 years.

Two more recent studies of radiation therapy patients indicate that for protracted exposure, ovarian function may be maintained after larger doses. Horning et al. (1981) reported on a group of 19 women treated with protracted pelvic irradiation for Hodgkin's disease. All received greater than 30 Gy to the ovary, with 18 receiving greater than 40 Gy, by standard protocol. Their median age at treatment was 22 years (range 13 to 28 years). Of ten patients desiring and capable of becoming pregnant, seven had normal live births at an average of 48 months after irradiation (range 37 to 100 months). These results indicate that for protracted exposure, the D_{50} for permanent suppression of ovulation may exceed 30 to 40 Gy.

Table 2.20

Effects of Ionizing Radiation on Ovarian Function[a,b,c]

Ovarian Dose (Gy)	Results
0.6	No deleterious effect.
1.5	No deleterious effect in young women; some risk for ovulatory suppression in women older than 40.
2.5-5.0	In women aged 15-40, 60% suffer permanent ovulatory suppression; remainder may suffer temporary amenorrhea. In women older than 40, 100% have permanent ovulation suppression.
5.0-8.0	In women aged 15-40, 60-70% suffer permanent ovulatory suppression; remainder may experience temporary amenorrhea. No data available for women over 40.
>8.0	100% permanent ovulatory suppression.

[a]Based on Damewood and Grochow (1986). Unpublished literature review by Dr. Joseph A. Watson (1987).

[b]These dose effects are consistent with those previously published (UNSCEAR, 1982).

[c]Those under 15 years of age are presumed to be of similar sensitivity as the 15-40 years age group.

Table 2.21

Median Dose Estimates (D_{50}) and Response Curve Shape Parameter (V) for Two-Year Suppression of Sperm Count in Males and Permanent Suppression of Ovulation in Females

Sex	Parameter	Brief Exposure[a]
Female	D_{50}	3.5
	Lower Bound[b]	2.5
	Upper Bound[b]	4.5
	Shape	3
	Lower Bound[b]	2
	Upper Bound[b]	4
	Threshold (Gy)	0.6[c]
	Lower Bound[b]	0.2
	Upper Bound[b]	1.0
Male	D_{50} (Gy)	0.7[d]
	Lower Bound[b]	0.6
	Upper Bound[b]	0.8
	Shape	10[e]
	Lower Bound[b]	9
	Upper Bound[b]	11
	Threshold	0.3[f]
	Lower Bound[b]	0.2
	Upper Bound[b]	0.4

[a]Brief exposure implies dose rates greater than or equal to 0.06 Gy/hr. Protracted exposure implies dose rates less than 0.06 Gy/hr. Model parameters were not developed for protracted exposure.

[b]Judgmental upper and lower bounds based on exploratory analysis of limited data.

[c]Based on data in Table 2.20.

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

[e]Based on data of Thorsland and Paulson (1972), Rowley et al. (1974), Sandermann (1966), and Hahn et al. (1982).

[f]Based on data in Table 2.22.

Husseinzadah et al. (1984) showed that ovarian function, as measured by gonadotropin levels, was maintained in women receiving pelvic irradiation if the ovaries received as much as 8.0 Gy.

Because protracted doses of tens of Gy to the ovary could not occur in a nuclear reactor accident without also having a lethal dose to the bone marrow, model parameters for permanent suppression of ovulation after protracted exposure were not developed.

2.2.8.2 Early Radiation Effects on the Testis

The testis is also quite sensitive to radiation. A detailed review on the effects of radiation and chemotherapy on testicular function has been published (Damewood and Grochow, 1986). Table 2.22 presents a summary of the findings. Doses as small as 0.1 Gy have caused temporary oligospermia (diminution of sperm count). Doses of 2 to 6 Gy or more are required to permanently suppress sperm count. The dose required to reduce the Type B spermatogonia to 37 percent of the initial number has been estimated to be only about 0.2 Gy. Recovery time is dose dependent and may require many years after exposure to large doses.

Two recent articles on testicular function after radiation therapy are consistent with the effects noted in Table 2.22. Berthelsen (1984) reported the effect of scattered radiation (0.2 to 1.3 Gy) reaching the remaining testicle of 34 patients following removal of the contralateral testicle for testicular cancer. Sperm counts and serum FSH levels, which are a sensitive index of germ cell depletion, were measured. The scattered radiation doses caused azoospermia in more than two-thirds of the patients. One to five years after treatment, the sperm counts were still reduced and FSH levels were elevated.

Shapiro et al. (1985) reported on the changes in testicular function as measured by hormonal alterations (serum FSH and LH levels) following radiotherapy in 27 males with soft-tissue sarcoma. Only patients with less than 0.5 Gy of scattered radiation showed an early complete recovery in hormonal levels; patients receiving 0.5 to 2 Gy or greater than 2 Gy did not return to normal hormonal levels within a 30 month follow-up.

The testis is unusual in that fractionated exposure may lead to slower recovery 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).

The 23 Japanese fishermen previously cited, who were exposed to weapons testing fallout, were estimated to have received 1.7 to 6.9 Gy of gamma rays over 14 days. Their sperm counts were severely depressed. Recovery of spermatogenesis began by 2 years and most men fathered healthy children (Kumatori et al., 1980; Freedman and Keehan, 1966; UNSCEAR, 1982). The testes of the fatal case (40-year-old with a dose of 5.1 to

Table 2.22

Effects of Fractionated Testicular X-Irradiation on Sperm Count[a]

Testicular Dose (Gy)	Results
0.1-0.3	Temporary oligospermia.
0.3-0.5	100% temporary aspermia from 4-12 months post-irradiation. Full recovery by 48 months.
0.5-1.0	100% temporary aspermia from 3-17 months. Full recovery beginning at 8-38 months.
1-2	100% temporary aspermia at 2-15 months. Recovery beginning at 11-20 months.
2-3	100% aspermia beginning at 1-2 months. No recovery observed up to 40 months.

[a]Based on Damewood and Grochow (1986), Ash (1980), Sanderman (1966), Spriser et al. (1973), and Hahn et al. (1976). No attempt was made to allow for variation in the mode of fractionation (Ash, 1980). Unpublished literature review by Dr. Joseph A. Watson.

These dose effects are consistent with those previously published (UNSCEAR,1982).

5.9 Gy) who died 206 days after the initial exposure were markedly atrophic. Spermatogonia were extremely depleted and, in some areas, were completely lacking. No sperm were found within the lumen of either the seminiferous tubules or epididymus.

Parameters of the dose-effect curve for two-year suppression of sperm count in males are given in Table 2.21.

2.2.9 Fetus

2.2.9.1 Nature of 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). Laboratory animals are most sensitive to the lethal effects of radiation before uterine implantation. It is likely that this radiosensitive preimplantation stage is also present in humans. However, it has been argued that the disparity in the timing of intrauterine development between women and laboratory animals may make the intra-species extrapolation of data invalid (Mole, 1982).

Congenital malformations resulting from intrauterine irradiation in humans are the central nervous system effects, microencephaly (i.e., small head circumference) and eye malformation (Brent, 1980). The greatest sensitivity to the effects of irradiation is in the early organogenesis stage of the embryo. Recent observations on Japanese atomic bomb survivors suggest that irradiation at 8 to 15 weeks of embryonic development carry the greatest risk for severe mental retardation (Otake et al., 1987). This gestational period coincides with the time of production of neurons in the cerebral hemispheres. No significant risk could be demonstrated for 0 to 7 weeks gestational period. For 16 to 25 weeks gestational period, the risk was less than for the 8 to 15 week period (Otake and Schull, 1984, 1987). Studies of humans exposed at random times during pregnancy to high doses of radiation indicate that microencephaly is the most common neonatal malformation (Miller and Mulvihill, 1976). An additional important finding was that no visceral, limb or other malformations were found unless the child exhibited microencephaly, readily apparent eye malformations or intrauterine growth retardation.

2.2.9.2 Dose-Effect Relationships

2.2.9.2.1 Reduced Head Circumference (Microencephaly)

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 2.9. Parameters associated with the dose-effect

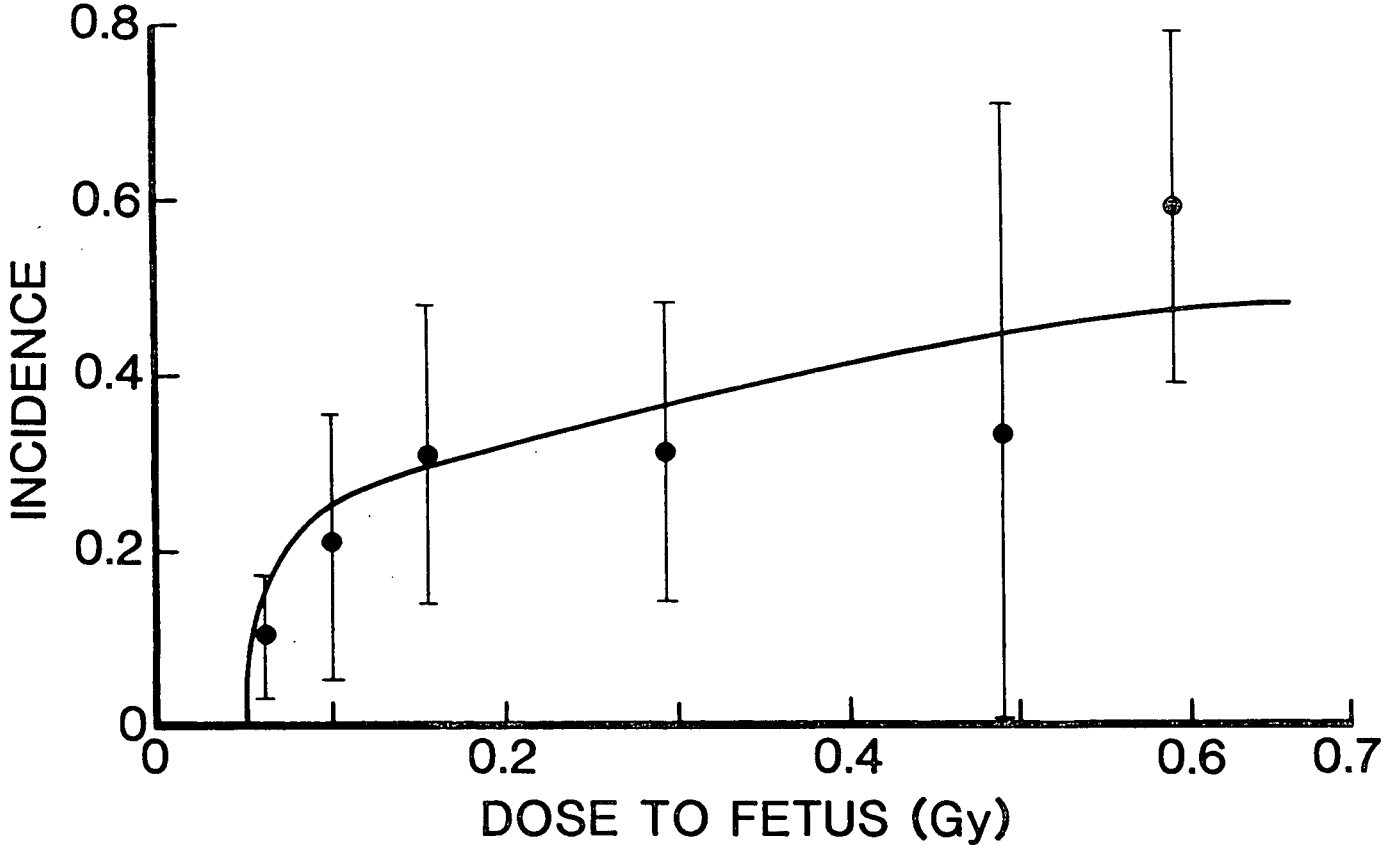

Figure 2.9. Dose-Effect Relationship for the Incidence of Reduced Head Circumference. Based on individuals exposed between 0 and 17 weeks of gestation in Hiroshima (Miller and Blot, 1972). The Dose, D_{50}, in Gy represents the dose to the fetus obtained using an organ dose to kerma ratio of 0.39 (BEIR III, 1980; Kerr, 1979). Error bars represent plus or minus two standard errors.

relationship are shown in Table 2.23. Ishimaru, Nakashima and Kawamoto (1984) re-examined the data on head circumference when the prenatal exposed Japanese cases were 18 years old. ICRP Publication No.49 (1986), in summarizing Ishimaru's results, states that head size diminishes linearly with estimated T65 dose. However, other relationships could also be easily accommodated by the data.

Neumeister and Wasser (1985), in a prospective clinical study of 100 children receiving diagnostic radiation exposure in utero, do not report the presence of reduced head circumference in the study group followed to 13 years of age. The reported doses were less than 0.18 Gy. Some information is available on the influence of dose rate on fetal malformations and suggests that lowering of dose rate or fractionating the dose leads to a sparing effect (UNSCEAR, 1977).

2.2.9.2.2 Mental Retardation

The prevalence of mental retardation among children irradiated in utero during the bombing of Hiroshima and Nagasaki was reported in the recent study of Otake et al. (1987). A child was considered mentally retarded if he or she was unable to perform simple calculations, to carry on a simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized. Most of the children considered mentally retarded were never enrolled in a public school; the few that were had IQ values less than 70. The highest prevalence of mental retardation occurred in those exposed at 8 to 15 weeks gestational age. Two additional publications by these investigators have appeared (Schull and Otake, 1984; Schull and Otake, 1986) and a detailed evaluation of the effect of irradiation on mental retardation has been carried out in ICRP No. 49 (1986).

When the mental retardation data were analyzed based on the new DS86 dosimetry, the following conclusions were arrived at by Otake et al. (1987):

1. The highest risk of radiation damage to the embryonic and fetal brain occurs during the 8 to 15 week period after fertilization under both the T65DR and DS86 dosimetry systems;

2. Damage to the 8 to 15 week fetus, expressed as severe mental retardation appears to be linearly related to the fetal absorbed dose, but to be linear-quadratically related to the dose for the intelligence scores data; and

3. Damage to the fetus 16 to 25 weeks after fertilization suggests the presence of a threshold, especially when based on DS86 dosimetry.

Two models were used by Otake et al. (1987) for severe mental retardation, a linear model, and an exponent-linear model (Tables 2.24

Table 2.23

Median Dose Estimate (D_{50}) and Response Curve Shape Parameter (V) for Small Head Size After Brief In Utero Exposure[a]

Parameter	Value	Lower Bound[b]	Upper Bound[b]
D_{50} (Gy)	0.73	0.5	0.8
Shape	0.4	0.2	1
Threshold	0.05[b]	c	c

[a]Based on data from Miller and Blot (1972; WASH 1400, 1975.) Rough estimates of D_{50} and threshold doses, based on DS86 dosimetry, can be obtained by multiplying the doses in the table by 1.193 (Otake et al., 1987). The new dosimetry should have a lesser impact on the shape parameter. 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.

[b]Judgmental.

[c]Lower and upper bound estimate for threshold undetermined.

Table 2.24

Relationship of Severe Mental Retardation to Fetal Dose, T65DR and DS86 Estimates[a], for Atomic Bomb Survivors Based on Linear Model

Gestational Age	MLE of Regression Coefficients a	b (Gy^{-1})
A. ALL CASES BASED ON T65DR		
All gestational ages	0.0077 ± 0.0024	0.17 ± 0.04
8-15 weeks	0.0092 ± 0.0059	0.40 ± 0.08
16-25 weeks	0.0060 ± 0.0040	0.10 ± 0.06
B. SUBSAMPLES BASED ON DS86		
All gestational ages	0.0074 ± 0.0024	0.17 ± 0.04
8-15 weeks	0.0077 ± 0.0052	0.40 ± 0.08
16-25 weeks	0.0061 ± 0.0040	0.10 ± 0.06

[a]From Otake et al., 1987; MLE = maximum likelihood estimate.

Linear model: $P = a + bD$

and 2.25). Both models lead to similar results. Parameter estimates obtained for the two models for brief exposure are given in Tables 2.24 and 2.25 taken from Otake et al. (1987).

A number of investigators have questioned use of the linear dose-effect model for mental retardation; see, for example, reviews by Brent (1986) and Mole (1987). Neumeister and Wasser (1985) advocate that pregnancy should be continued following in utero exposures of below 100 mSv. However, their data is not adequate to address the issue of a radiation-dose threshold.

NCRP (1987) states that for irradiation at 8 to 15 weeks after fertilization, the probability of induction of mental retardation could be assumed to follow a linear relationship with dose, with no observed dose threshold. The linear model was used to obtain conservative estimates of risk. The slope of this linear relationship is approximately 0.4 Sv^{-1} over a fetal dose equivalent range of 0.01 to more than 2 Sv. Between the 16th and 25th week after conception, the risk of mental retardation is less and can be approximated by a linear model with a slope of about 0.1 Sv^{-1}.

Model parameters D_{50} and V for severe mental retardation are given in Table 2.26 and are based on the exponent-linear model in Table 2.25 and DS86 dosimetry. We have assumed that the parameter a used by Otake et al. (1987) accounts for effects not related to radiation exposure. In this case, the product bD represents the cumulative hazard for radiation-induced effects. The parameter b is related to the parameter D_{50} by expression.

$$D_{50} = \ln(2)/b$$

2.2.9.2.3 Prenatal Death

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 et al., 1986, 1987; Brent and Gorson, 1972).

Although irradiation of the preimplanted embryo does not lead to permanent growth retardation or malformations in surviving embryos at term, it does exhibit the lowest LD_{50} (Brent et al., 1987). Lethality from acute effects can be observed at term in the rat and mouse after exposure to 0.1 to 0.15 Gy of X rays on the first day of gestation. Lethality in the same time period has not been documented in humans. However, most human exposures to diagnostic X-rays do not exceed 0.1 Gy (Brent et al., 1987). While Brent and coworkers believe that the preimplanted human embryo is the stage most sensitive to embryolethality, their view is that "we will probably never be able to document this conclusion in the human population."

Table 2.25

Relationship of Severe Mental Retardation to Fetal Dose, T65DR and DS86 Estimates[a] for Atomic Bomb Survivors Based on Exponent-Linear Model

MLE of Regression Coefficients

Gestational Age	a	b (Gy^{-1})
A. ALL CASES BASED ON T65DR		
All gestational ages	0.0077 ± 0.0024	0.18 ± 0.05
8-15 weeks	0.0085 ± 0.0057	0.51 ± 0.14
16-25 weeks	0.0060 ± 0.0040	0.10 ± 0.06
B. SUBSAMPLES BASED ON DS86		
All gestational ages	0.0075 ± 0.0024	0.17 ± 0.04
8-15 weeks	0.0076 ± 0.0052	0.46 ± 0.12
16-25 weeks	0.0062 ± 0.0041	0.10 ± 0.06

[a]From Otake et al., 1987; MLE = maximum likelihood estimate.

Exponent linear model: $P = 1 - \exp[-(a + bD)]$.

Table 2.26

Median Dose Estimate (D_{50}) and Response Curve Shape Parameter (V) for Severe Mental Retardation Following Brief In Utero Exposure[a]

Gestational Age	D_{50} (Gy) Central Estimate	Lower Bound	Upper Bound	Shape Parameter[c]
All Ages	4.1 (4.2)[b]	1.5[d]	7.1[d]	1
8-15 weeks	1.5 (1.7)[b]	1.0[e]	3.1[e]	1
16-25 weeks	7.1 (7.1)[b]	3.1[f]	10[g]	1
26+ weeks	-[h]	-	-	-

[a]Based on Otake et al. (1987), with DS86 dosimetry and use of dose to uterus as estimate of dose to fetus. Neutron doses assumed negligible.

[b]Corresponding estimates of D_{50} based on linear model in Table 2.24.

[c]Based on exponent-linear model (Table 2.25) with parameter a accounting for effects not related to irradiation. Affects of uncertainty in shape parameter assumed accounted for with upper and lower bounds on D_{50}.

[d]Lower bound same as for 8-15 weeks; upper bound same as for 16-25.

[e]Based on 95 percent confidence interval for parameter b in Table 2.26.

[f]Same as upper bound for 8-15 weeks.

[g]Judgmental estimate.

[h]Assumed negligible (Otake et al., 1987).

Model parameters for embryolethality in the human female are based on extrapolation from animal data (Brent et al., 1986, 1987; Brent and Gorson, 1972). Model parameters given in Table 2.27 were estimated from information provided by Brent et al. (1987).

2.2.10 Eyes

It is well known that exposure to external ionizing radiation may result in posterior polar cataracts in man (Griffith et al., 1985). The primary injury occurs in the germinative zone of the lens epithelium, which is a single layer of cells under the capsule on the anterior face of the lens. The cells of the germinative zone continue to divide throughout life. However, the rate of division decreases with increasing age. The daughter cells differentiate into lens fibers that make up the body of the lens. Ionizing radiation permanently damages cells which leads to abnormal lens fibers. The cellular debris and abnormal fibers gradually move from the equator to the posterior pole of the lens where they form a plaque of material that is opaque to light. The higher rate of cell division at a young age correlates with the greater sensitivity of this age group (Cogan and Donaldson, 1951; Von Sallmann, 1952; Griffith et al., 1985).

Griffith et al. (1985) point out that some of the peculiarities of radiation cataracts arise from the fact that new lens fibers are laid down throughout life by the slow proliferation of epithelium. Because the lens is enclosed in a capsule which is impermeable to cells, no phagocytic system exists. Thus, a damaged epithelial cell contributes permanent damage to the lens by the formation of damaged fiber. Because of continuous growth with age, the damaged cells and fibers get pushed under the capsule to the posterior pole of the lens, leading to formation of a posterior polar cataract.

Different components of the eye have different radiosensitivities (Parsons et al., 1983). The lens is especially sensitive when uniformly irradiated (Griffith et al., 1985; UNSCEAR, 1982). Epithelial tissues around the eye seem to have radiosensitivity similar to that of skin. For induction of cataracts, there is a dose-effect relationship which varies with follow-up time (Choshi et al., 1983). The latent period varies from about half a year to about 35 years, with an average of about 2 to 3 years (UNSCEAR, 1982; Hump, 1947; Cogan and Dreisler, 1953; Merriam and Focht, 1957). 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 percent. Protraction or fractionation of the dose leads to a sparing effect. A dose of 10 Gy delivered over 3 to 12 weeks caused cataracts in 75 percent of those exposed, and 14 Gy led to 100 percent 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., 1979; Bendel et al., 1978).

Table 2.27

Median Dose Estimate (D_{50}) and Response Curve Shape Parameters (V) for Embryolethality[a]

Embryonic Age (Days)	Developmental Period	Parameter	Brief Exposure Estimate
0-18	Preimplantation[b]	D_{50} (Gy)	1.0
		Lower Bound[c]	0.6
		Upper Bound	1.4[d]
		Shape[e]	2
		Lower Bound[f]	1.5
		Upper Bound[f]	2.5
		Threshold (Gy)	0.1[g]
		Lower Bound[f]	0
		Upper Bound	0.6[h]
18-150	Growth and Development	D_{50} (Gy)	1.5[i]
		Lower Bound	1.0[j]
		Upper Bound	2.0[k]
		Shape	3.0[l]
		Lower Bound[f]	2.0
		Upper Bound[f]	4.0
		Threshold (Gy)	0.4[m]
		Lower Bound	0.25[n]
		Upper Bound	0.5[n]
150-term	Late Fetus to Term	D_{50} (Gy)[o]	--
		Shape[o]	--
		Threshold (Gy)[o]	--

[a]Based on data in Table 2.21 taken from Brent et al. (1987). Brief exposure implies dose rate greater than or equal to 0.06 Gy/hr.
[b]Based on embryonic age interval 1-5 days.
[c]Lower bound judgmental.
[d]Same as for embryonic age interval 18-36 days.
[e]Reported minimum lethal dose was used as an estimate of the dose associated with a 1% incidence of death to estimate the shape parameter: Shape Parameter = 4.23/ln(D50/D01)
[f]Judgmental bounds.
[g]Same as minimum lethal dose.
[h]Same as lower bound for D50.
[i]Midrange for embryonic age intervals 18-36 days, 36-50 days, and 50-150 days.
[j]Same as for embryonic age interval 50-150 days.
[k]Same as for embryonic age interval 36-50 days.
[l]Based on equation in footnote e.
[m]Midrange of 0.25-0.5 Gy interval for minimum lethal dose.
[n]From reference cited in footnote a.
[o]Same as for the mother (see Table 2.7).

Deeg and coworkers (1984) examined 277 patients, who were followed for 1 to 12 years after marrow transplantation, for cataracts. In preparation for the transplantation, 96 individuals with aplastic anemia were conditioned with chemotherapy only (usually cyclophosphamide), while 181 patients (2 with aplastic anemia and 179 with a hematologic malignancy) were conditioned with a regimen of total-body irradiation (^{60}Co) and chemotherapy. Either a single 10 Gy dose or fractionated exposure (6 to 7 days, 12 to 15.8 Gy) were given. Kaplan-Meier product limit estimates of the incidence of cataracts for patients given a single-dose or fractionated exposure were 80 percent and 18 percent, respectively (Deeg et al., 1984). On the basis of proportional hazard regression analyses, patients receiving a single-dose had a relative risk of developing cataracts that was 4.7-fold higher than in patients given fractionated exposures. Additional significant risk factors that were identified include the chronic use of steroids and diagnoses of acute lymphoblastic or chronic myelogenous leukemia.

Choshi and coworkers conducted a two-year (1978 to 1980) ophthalmologic study of age- and radiation-related ophthalmologic lesions among the atomic bomb survivors in Hiroshima and Nagasaki (Choshi et al., 1983). The study sample in both cities was made up of all persons exposed to 1+ Gy, their controls, and all other persons with a previous record of axial opacities or posterior subcapsular changes. Increasing lenticular opacities, other lens changes, and loss of visual acuity and accommodation occurred with increasing age in both the exposed and control groups. Effects observed in controls were judged to be a manifestation of the normal aging process. A highly significant excess risk for all ages in the 3+ Gy Hiroshima group, in comparison to controls, was observed for both axial opacities and posterior subcapsular changes, but not in the Nagasaki group. A strong radiosensitive aging effect for persons in Hiroshima who were under 15 years old at the time of the bombing was observed for both axial opacities and posterior subcapsular changes. Their results for the Hiroshima group are given in Table 2.28.

Dose-effect model parameters are summarized in Table 2.29. Because protracted doses required to induce cataracts would also be associated with lethal doses to the bone marrow for the types of exposures anticipated following a nuclear power plant accident, no model parameters are provided for protracted exposure.

2.3 Uncertainties in Risk Estimates

There are several sources of uncertainty in risk estimates derived from this chapter. The major potential sources of uncertainty are: (1) statistical errors in parameter estimates derived from weak (small) data bases; (2) systematic errors associated with the dose-response models; (3) uncertainty in cross-species extrapolation; (4) uncertainty about dose protraction effects; (5) uncertainty in dose estimates; (6) limitations in our understanding of the effects of medical treatment;

Table 2.28

Relative Risk by Age Group for Axial Opacities in Survivors of the Atomic Bombing in Hiroshima[a]

	<50 Years Old		50-59 Years Old		60+ Years Old	
Dose Group (Gy)	Relative Risk[b]	Significance[c]	Relative Risk	Significance	Relative Risk	Significance
1.0-1.99	1.14	N.S.	0.86	N.S.	0.96	N.S.
2.0-2.99	2.10	N.S.	1.24	N.S.	1.35	*
3+	4.75	***	2.3	**	1.4	**

[a]Based on Table X of Choshi et al. (1983). Doses represent tentative 1965 dose estimates revised (T65DR) on bases of relocated epicenter. No similar information is currently available, based on DS86 dosimetry.

[b]Relative risk based on prevalence data. This differs from relative risk based on proportional hazard model.

[c]Significance levels: N.S.; P>0.10; *P<0.05; **P<0.01; ***P<0.001.

Table 2.29

Median Dose (D_{50}) and Response Curve Shape Parameter (V) for Cataracts After Irradiation

Parameter	Units	Brief Exposure[a]
D_{50}	Gy	3.1
Lower Bound[c]	Gy	2
Upper Bound[c]	Gy	4
Shape[b]		2
Lower Bound[c]		1
Upper Bound[c]		3
Threshold[c]	Gy	1
Lower Bound[c]	Gy	0.5
Upper Bound[c]	Gy	1.5

[a]Brief exposure: Dose rates greater than or equal to 0.06 Gy/hr. Central estimate for D_{50} taken from Langham et al. (1965). For protracted exposure at dose rates less than 0.06 Gy/hr, D_{50} and threshold doses may be 2 to 5 times larger (Griffith et al., 1985; UNSCEAR, 1982; Deeg et al., 1984).

[b]Based on data from Langham et al. (1965) for protracted exposure.

[c]Judgmental estimates.

(7) limitations in our understanding about the distribution of radiosensitivity among the population; (8) uncertainty in threshold dose; and (9) uncertainty in how to deal with nonuniform exposure.

Some dose-effect functions were developed from analysis of human data. The three main types of data used were those from accidents, radiation therapy, and data from victims of the bombings 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 the data are used to estimate the risks in mixed populations of adults and children, men and women, and healthy and diseased individuals. Interpretation of data from accidental overexposure is often further complicated by limited knowledge of the doses and dose rates to critical organs, by nonuniform dose distribution, and by the medical care received. Medical care, which may influence risk in significant but imprecisely-understood ways, also introduces uncertainties in our estimates of the risk.

Data from human therapeutic exposure have been used to derive some of the dose-response functions. Often therapeutic data involve larger numbers of subjects, and because of this, Poisson uncertainties are 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 derive, from the parameter estimates obtained from analysis of therapeutic data, those parameters needed to predict risk in the circumstances of interest. Interpretation of therapeutic data is further complicated because the individuals irradiated may not be representative of healthy individuals, and may have received chemotherapy as well as supportive and intensive treatment.

Data from the victims 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 a high dose rate. Third, the dosimetry is somewhat uncertain. Fourth, interpretation of the data is complicated because of blast and burn effects. Major advantages of this data set the relatively large number of individuals exposed, a wide range of doses, and detailed followup.

Where adequate human data were unavailable, dose-response functions were based extrapolations from animal data. In the animal experiments, relatively large numbers were involved and uncertainty in dose was relatively small. However, there is an inevitable uncertainty in extrapolating from one species to another.

Uncertainties are potentially introduced by our adjustment of the parameters of dose-response functions. Ideally, it should 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 percent, 50 percent, and 95 percent 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:

$$R = 1 - \exp[-0.693(D/D_{50})^{V}] \quad ,$$

where D_{50} and V are imprecisely known, one would first estimate probability density functions for D_{50} and 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; if the parameter estimates are correlated, one must have an estimate of the degree of correlation.

The available data from accidental overexposures were reviewed in an attempt to estimate confidence intervals. A logistic regression analysis was performed using the data from Smith's (1983) review of 35 individuals with accidental overexposures, along with data from Ewing's sarcoma patients receiving radiation therapy (Mole, 1984). These data include accident victims for more than 10 separate events including the 1974 and 1977 ^{60}Co gamma radiation exposure incidents in New Jersey (Barlotta, 1980). Almost all of these individuals received supportive treatment and some received bone marrow transplants. Two individuals who received highly nonuniform exposures were excluded from the analysis.

The results suggest LD_{50}s for total-body irradiation with 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. The predicted LD_{50}s and hazard function slopes are consistent with the Chernobyl accident data.

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 percent 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 for the supportive treatment category.

In view of the ambiguities inherent in interpretation of these analyses, we abandoned the formal approach and concentrated instead upon providing upper and lower bounds on model parameters and thresholds that can be used in computer simulation studies to investigate the impact of uncertainty.

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3.0 LATE SOMATIC EFFECTS

E. S. Gilbert, Battelle Pacific Northwest Laboratories

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 in 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 12 years after birth for leukemia, and 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, and because very recent data suggest attenuation of these risks with time, for most central and lower bound estimates a single risk coefficient based on combined data for all exposure ages has been used to calculate lifetime risks. In most cases, upper bound estimates have been obtained using a larger relative risk coefficient for those exposed under age 20 than for those exposed at older ages. 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 3.0. 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 most cancer types 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 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 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 3.0 we have

Table 3.0

Estimates of Lifetime Risk of Mortality from Low-LET Radiation Received at Low Dose Rates (<0.05 Gy/d) Based on the Linear Term of the Linear-Quadratic Function

	Number of Deaths (per 10^4 per Gy)			Years of Life Lost (per 10^4 per Gy)		
Effect	Lower	Central	Upper	Lower	Central	Upper
Leukemia	4.8	14	48	168	505	1,682
In Utero	1.2	1.2	3.0	80	80	200
Bone Cancer	0.2	0.6	2.1	7	22	75
Breast Cancer	4.4	60	87	97	955	1,452
Lung Cancer	5.3	20	245	100	288	3,606
GI Cancer	9.1	57	327	222	661	3,953
Thyroid Cancer	7.2	7.2	7.2	203	203	203
Other Cancer	5.1	29	169	124	378	2,329
In Utero	1.2	1.2	3.0	80	80	200

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 3.0.

Editor's Note: Since the first edition of NUREG/CR-4214 was published, the Report of the National Institutes of Health ad hoc Working Group to Develop Radioepidemiological Tables (NIH Report, 1985) has been issued, and new relevant data have become available, including an additional four years of follow-up on the Japanese atomic bomb survivors. The revisions made in this second edition represent an attempt to give consideration to this additional information, and to examine certain aspects of the model that pose practical problems (for implementing computer programs designed to calculate estimates for specific accident scenarios). The revisions are not intended to represent a complete updating of the report that takes into account all recent data in an optimal way. In particular, no attempt has been made to consider recent data in determining quantitative risk coefficients for various cancer categories. This latter task does not seem sensible until analyses based on revised dosimetry for the Japanese atomic bomb survivors are available.

3.1 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 weak 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 in 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 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. In preparing the second edition of this report, models used in a report of the National Institutes of Health (1985) 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 Lowe and Mendelsohn (1981) and Kerr (1981). At the time of preparation of the second edition of this report, this dose reassessment has been completed, and initial analyses comparing results based on the tentative 1965 dosimetry system (T65D) and on the revised dosimetry system (DS86) have been reported (Preston and Pierce, 1987). These analyses make it clear that the effect of revised dosimetry on risk estimates will be strongly dependent on the estimated RBE for neutrons, which cannot be reliably determined from the revised dosimetry, and on the shielding provided by the body for specific organs of interest. Because a complete assessment of these recent data has not yet been reported and evaluated, we do not believe it is appropriate to speculate further in this report concerning the effects of revised dosimetry on estimates based on the Japanese data. Thus estimates are based on T65D dosimetry as described and used by Kato and

Schull (1982), Wakabayashi et al. (1983), and Kerr (1979). These risk estimates must be reevaluated when analyses based on the revised dosimetry have been completed, but based on the results given in Preston and Pierce (1987), it appears unlikely that the modified dosimetry will increase risk estimates by more than a multiplicative factor of two.

One effect of the dose revision that has been clearly 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 known to be more appropriate than previously thought.

Analyses of updated Japanese data will include not only attention to the effects of revised dosimetry on risk coefficients, but also will address questions related to the form of the dose-response function, and on the persistence of effects with time from exposure. In the next year or two the BEIR V Committee will provide an evaluation of the most up-to-date analyses of the Japanese data, as well as other recent data. Based on this evaluation, it is possible that some of the modeling assumptions that have been used in this report will need to be reconsidered and revised. Thus it is strongly recommended that the estimates provided by this report be reevaluated when the BEIR V report becomes available.

3.2 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 3.3. A summary of the model in tabular form is given in Table 3.1.

For each cancer site considered, three lifetime risk estimates are determined: a central estimate, an upper bound, and a lower bound. The upper estimates are based on a linear model, while, in most cases, the central and lower estimates are obtained by modifying the linear estimates as described in Sections 3.2.1 and 3.2.3.

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 3.2 and 3.3, are obtained from epidemiological data as described in Section 3.4. 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 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

Table 3.1

Summary of the Model Used to Determine Upper Bound, Central, and Lower Bound Lifetime Risk Estimate for Mortality and Incidence[a,b]

	Risk Estimate		
Effect	Upper Bound	Central	Lower Bound
Cancers Due to Other Than *In Utero* Exposure			
Leukemia and Bone	Use absolute linear estimate	Modify upper bound by reduction factors in Table 3.4	Modify upper bound by reduction factors in Table 3.4
Breast	Use age-specific relative linear estimate	Use non-age-specific relative linear estimate	Modify absolute linear estimate by reduction factors in Table 3.4
Lung	Use age-specific relative linear estimate	Modify non-age-specific relative linear estimate by reduction factors in Table 3.4	Modify absolute linear estimate by reduction factors in Table 3.4
Gastrointestinal	Use age-specific relative linear estimate	Modify non-age-specific relative linear estimate by estimate reduction factors in Table 3.4	Modify absolute linear estimate by reduction factors in Table 3.4
Thyroid[c]	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate
Skin	Use absolute linear estimate	Modify upper bound by reduction factors in Table 3.4	Modify upper bound by reduction factors in Table 3.4

Table 3.1

Summary of the Model Used to Determine Upper Bound, Central, and Lower Bound Lifetime Risk Estimate for Mortality and Incidence[a,b]
(Concluded)

	Risk Estimate		
Effect	Upper Bound	Central	Lower Bound
Other Cancers	Use age-specific relative linear estimate	Modify non-age-specific relative linear estimate by reduction factors in Table 3.4	Modify absolute linear estimate by reduction factors in Table 3.4
Benign Thyroid Nodules[d]	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate
Cancers Due To *In Utero* Exposure	Use absolute linear estimate	Use absolute linear estimate multiplied by 0.4	Use central estimate

[a] The linear estimates referred to are given in Table 3.2 (mortality) and Table 3.3 (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, ne third as effective for the central estimate, and one tenth as effective for the lower bound (see Section 3.4.6).

[d] ^{131}I is assume 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 3.4.6).

Table 3.2

Risk Coefficients and Lifetime Risk Estimates for Mortality from Several Cancer Types

Effect	Period at Risk (yrs)	Risk Coefficient (Gy^{-1}) Absolute (per 104 PY)	Risk Coefficient (Gy^{-1}) Relative (%)	Number of Deaths[a] (per 10^4 per Gy) Absolute	Number of Deaths[a] (per 10^4 per Gy) Relative	Years of Life Lost[a] (per 10^4 per Gy) Absolute	Years of Life Lost[a] (per 10^4 per Gy) Relative
Leukemia	2-27	2.2	-	48	-	1682	-
In Utero[b]	0-12	25[f]	-	3[g]	-	200	-
Bone Cancer	2-27	0.1	-	2	-	75	-
Breast Cancer							
Age-specific	10-life	-	103[d], 42[d]	-	87[e]	-	1,452
Non-age-specific	10-life	2.6	45	43[e]	60[e]	973	955
Lung Cancer							
Age-specific	10-life	-	111[d], 37[d]	-	245	-	3,606
Non-age-specific	10-life	2.0	18	53	67	999	959
GI Cancer							
Age-specific	10-life	-	117[d], 39[d]	-	327	-	3,953
Non-age-specific	10-life	2.7	39	91	189	2,223	2,202
Thyroid Cancer[c]	5-life	0.25[d], 0.12[d]	-	7	-	203	-
Other Cancer							
Age-specific	10-life	-	60[d], 20[d]	-	169	-	2,329
Non-age-specific	10-life	1.5	20	50	96	1,235	1,260
In Utero[b]	0-12	28[f]	-	3[g]	-	200	-

[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 3.1 to obtain central and lower estimates. Absolute and relative risk projection models are described in Section 3.3.2.

[b]These estimates may be too high because of recent improvements in cure rates. See Section 3.3.3.

[c]Thyroid cancer mortality risk coefficients have been obtained by reducing the incidence coefficients given in Table 3.3 by a factor of ten. See Section 3.3.3 and 2.6.

[d]In each case the first coefficient applies to those under age 20 at exposure and the second coefficient applies to those 20 and over at exposure.

[e]These lifetime risk estimates apply to the entire population and are one-half the risks for females.

[f]These coefficients apply to the in utero population only.

[g]These lifetime risk estimates apply to the entire population and are 1 percent of the in utero risks.

Table 3.3

Risk Coefficients and Lifetime Risk Estimates for Incidence of Several Cancer Types

Effect	Period at Risk (yrs)	Risk Coefficient (Gy^{-1}) Absolute (per 104 PY)	Risk Coefficient (Gy^{-1}) Relative (%)	Number of Cases[a] (per 10^4 per Gy) Absolute	Number of Cases[a] (per 10^4 per Gy) Relative	Years With Cancer[a] (per 10^4 per Gy) Absolute	Years With Cancer[a] (per 10^4 per Gy) Relative
Breast Cancer							
Age-specific	10-life	-	103[b], 42[b]	-	254[c]	-	3,204
Non-age-specific	10-life	7.4	45	124[c]	172[c]	1,796	2,057
Lung Cancer							
Age-specific	10-life	-	111[b], 37[b]	-	273	-	501
Non-age-specific	10-life	2.2	18	59	74	100	129
GI Cancer							
Age-specific	10-life	-	117[b], 39[b]	-	561	-	3,138
Non-age-specific	10-life	4.6	39	156	322	1,564	1,719
Thyroid Cancer	5-life	2.5[b], 1.25[b]	-	72	-	2,026	-
Skin Cancer	10-life	2.0	-	67	-	1,635	-
Other Cancer							
Age-specific	10-life	-	60[b], 20[b]	-	337	-	2,981
Non-age-specific	10-life	2.9	20	98	187	1,152	1,530
Benign Thyroid Nodules	10-life	9.3, 4.7	-	268	-	-	-

[a]These risks are based on a linear model and in most cases must be modified as described in Section 3.2.1 and as summarized in Table 3.1 to obtain central and lower estimates. Absolute and relative risk projection models are described in Section 3.3.2.

[b]In each case the first coefficient applies to those under age 20 at exposure and the second coefficient applies to those 20 and over at exposure.

[c]These lifetime risk estimates apply to the entire population and are one-half the risks for females.

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 3.3.2; details regarding calculations are given in Section 3.6.

For leukemia and bone cancer, after a 2-year latent period risks are assumed to persist for a period extending 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 3.3.2 and 3.6.

Because of the difficulty in obtaining reliable estimates for those who are young at exposure, and because very recent data suggest attenuation of these risks with time, for most central and lower bound estimates a single risk coefficient based on combined data for all exposure ages has been used to calculate lifetime risks. In most cases, upper bound estimates have been obtained using a larger relative risk coefficient for those exposed under age 20 than for those exposed at older ages. The effect of age at exposure is discussed in Section 3.3.6.

3.2.1 Central Estimates for Latent Cancer Mortality and Incidence

For most cancer types, the central estimates are obtained by modifying the non-age-specific linear risk estimates presented in Tables 3.2 and 3.3 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 3.3.1. 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 3.3.2, 3.4.2, and 3.4.3). However, for other cancers (e.g., gastrointestinal cancers and a residual group of cancers later referred to as "other" cancers) the choice is less clear. While for these cancers relative risk is used in this report, for some purposes it may be appropriate to consider estimates based on the absolute risk model.

3.2.2 Upper Estimates

The upper estimates are 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 most cancer types also differs from the central estimate in that larger risk coefficients are used for those exposed under age 20 than for those exposed at older ages. 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 age at exposure (Section 3.3.6) and lung cancer (Section 3.4.4).

3.2.3 Lower Estimates

To obtain lower estimates, 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 estimates.

3.3 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.

3.3.1 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 provides 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 3.1. 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

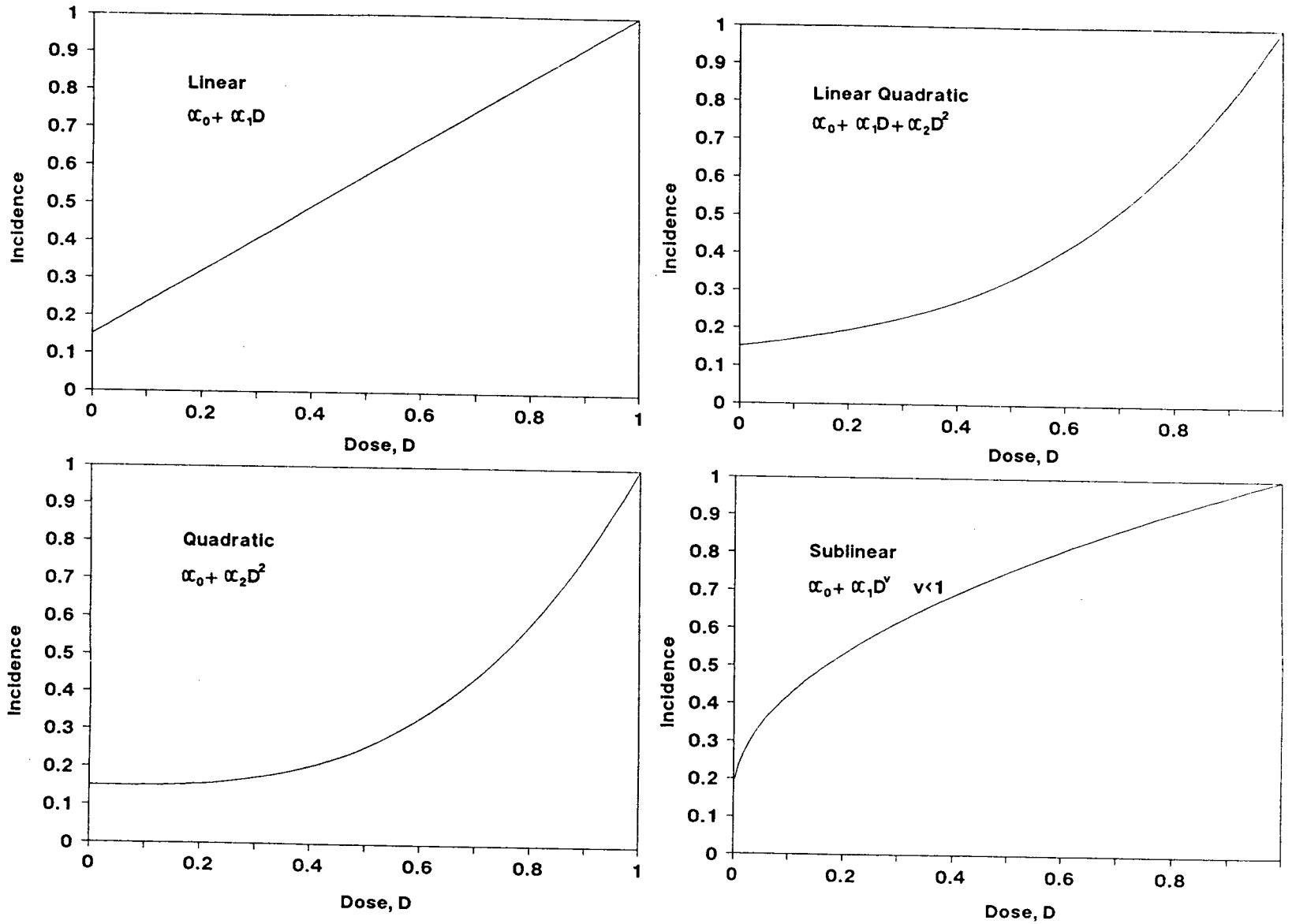

Figure 3.1. Alternate Dose-Response Curves (BEIR III [1980] Figure II-2 with modifications)

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 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, parameter a can be thought of as the reduction factor appropriate for very low exposures while parameter 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 $0.99D + 0.85D^2 = (0.44 + 0.38D)\ 2.24D$ 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 parameter 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) was to choose parameter a as the dose-rate reduction factor, or the limiting slope of the linear-quadratic function as the dose approaches zero, and to choose parameter 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., $\ll 0.05$ 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., $\gg 0.05$ 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. This function is not intended to provide a realistic description of the dose-response, but should still provide reasonable lower limits for cancer risks. Also it should be noted that a lower limit of zero for

most coefficients derived from populations exposed to low-LET radiation cannot be excluded by the data.

In BEIR III, a pure quadratic model 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 revisions in T65D doses.

The reduction factors to be used for the upper, central, and lower bound estimates for low-LET radiation are summarized in Table 3.4. In Table 3.5, these factors are applied to obtain estimates of risks for several cancer types resulting from chronic exposures at low dose rates. In Table 3.6, central estimates for exposures at several levels are presented.

Available epidemiological data are not adequate to obtain reliable estimates of all the 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)].

3.3.2 Projection of Risks Over Time

None of the populations on which estimates of health effects are based has yet been followed to the end of its life span. This does not present a serious problem for estimating the number of leukemia deaths, since evidence from Japanese atomic bomb survivors indicates that leukemia rates return to levels close 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 data on Japanese survivors (Kato and Schull, 1982; Wakabayashi et al., 1983; Preston et al., 1987) indicate that radiation-induced cancer risks persist at least for 37 years after exposure. Thus the use of a model in which risks are assumed to persist over an exposed individual's lifetime (the choice of BEIR III) 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. Because of this, the relative risk

Table 3.4

Reduction Factors for Central and Lower Estimates of Risk

Dose Rate[a]	Dose (Gy)	Risk Reduction Factor: Central Estimate[b,c]	Risk Reduction Factor: Lower Estimate[d]
Low	any	0.30	0.10
High	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]Dose rates <0.05 Gy per day are considered low. Dose rates ≥0.05 Gy per day are considered high.

[b]Central risk reduction factor is 0.30 + 0.47D, where D is in Gy.

[c]The risk reduction factor from the NIH Radioepidemiological Tables (NIH, 1985) could be represented approximately as 0.45 + 0.37D, where D is in Gy. This approach would yield risk estimates about 50 percent higher than our central estimates at low dose or at low dose rate. Their estimates of the risk at high dose and high dose rate would equal ours.

[d]Lower risk reduction factor is 0.10 + 0.60D, where D is in Gy.

Table 3.5

Central, Upper, and Lower Estimates 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	4.8	14	48	168	505	1,682
Bone	0.2	0.6	2.1	7	22	75
Breast	4.4	60[e]	87	97	955[e]	1,452
Lung	5.3	20	245[f]	100	288	3,606[f]
Gastrointestinal	9.1	57	327	222	661	3,953
Thyroid	7.2	7.2	7.2	203	203	203
Other	5.1	29	169	124	378	2,329
Cancers Due to *In Utero* Exposure						
Leukemia	1.2[g]	1.2[g]	3.0	80[g]	80[g]	200
Other	1.2[g]	1.2[g]	3.0	80[g]	80[g]	200

[a]With the exception of cancers resulting from *in utero* exposure, these estimates are obtained by modifying the absolute linear estimates in Table 3.2 by the factor 0.10.

[b]With the exception of breast cancer, thyroid cancer and cancers resulting from *in utero* exposure, these estimates are obtained by modifying non-age-specific linear estimates in Table 3.2 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 age-at-exposure-specific (except for leukemia and bone cancer) linear estimates.

[e]Non-age-at-exposure-specific linear estimate.

[f]Based on a larger relative risk coefficient than the central estimate.

[g]These estimates are obtained by modifying the upper bound estimates by 0.4 (see Section 3.4.B).

Table 3.6

Central Estimates of Lifetime Risks of Mortality
Resulting From Exposure to Several Doses[a]

	Number of Deaths Per 10^4 Population					Years of Life Lost Per 10^4 Population				
	Dose (Gy)					Dose (Gy)				
Effect	0.01	0.10	0.50	1.0	2.0	0.01	0.10	0.50	1.0	2.0
Leukemia	0.1	1.2	9.1	26	68	3.5	41	318	906	2,354
In Utero	0.01	0.1	0.6	1.2	2.4	0.8	8.0	40	80	160
Bone Cancer	0.006	0.07	0.6	1.7	4.3	0.2	2.6	20	58	150
Breast Cancer	0.6	6.0	30	60	120	9.5	95	477	955	1,909
Lung Cancer	0.2	2.3	18	52	134	2.9	34	259	739	1,918
GI Cancer	0.6	6.6	51	146	378	6.6	77	594	1,695	4,404
Thyroid Cancer	0.05	0.5	2.4	4.8	9.6	1.4	14	68	135	271
Other Cancer	0.3	3.4	26	74	192	3.8	47	340	970	2,520
In Utero	0.01	0.1	0.6	1.2	2.4	0.8	8.0	40	80	160

[a]With the exception of breast cancer, thyroid cancer, and cancers resulting from in utero exposures these estimates are obtained by modifying non-age-specific linear estimates presented in Table 3.2 by the reduction factors in Table 3.4

model yields larger numbers of new cases or of deaths for the years beyond the follow-up period.

Data on Japanese survivors and the ankylosing spondylitis patients (Smith and Doll, 1982) indicate that radiation-induced 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 Tables 3.7.1 and 3.7.2), 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 taken into account. By contrast, excess (or absolute) risks showed increasing trends with increased time from exposure.

Table 3.7.1

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

[a]ATB = at the time of the bombing, 1945.

Even though there is evidence that as a population ages, the risk of radiation-induced cancer increases approximately in proportion to spontaneous risks, this pattern may not persist for a lifetime. Very recently, several studies have provided some support for a decline in relative risks with time from exposure. The strongest support for this decline comes from a recent analysis of data on British ankylosing spondylitis patients by Darby and associates (1987). In this study, the proportional increase in cancer mortality was only 7 percent for the period 25 years or more after treatment compared with 38 percent for the period 5 to 24 years after treatment. The decline tended to be larger for those younger at exposure, but the trend with age at exposure was not statistically significant. Lung cancer was the strongest contributor, but the decline was not restricted to this cancer site.

Table 3.7.2

Absolute Risk By Age ATB[a] (Excess Deaths/10^4 PY/Gy, 1950-1978)
(Kato and Schull [1982] Table V)

		Age at Death					
Cancer Type	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)[b]	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.

Recent analyses of the atomic bomb survivors (Preston et al., 1987) indicate that risks persist through 1982 (38 years of follow-up), but indicate a decline in the relative risk coefficient over time for those exposed early in life. Preston and Pierce (1987) have analyzed atomic bomb survivor data through 1985. The principal purpose of this analysis was to address changes in risk estimates resulting from revised dosimetry, and thus the persistence of risks over time was not analyzed specifically. However, calculations based on summarized data provided in this report indicate that for those exposed under age 20, the relative risk observed 35 years or more after exposure had dropped to about the level for those exposed at older ages. There was no indication, however, of a decline in relative risks for those exposed at older ages.

Finally, in a recent analysis of U.S. uranium miners, Hornung and Meinhardt (1987) found that after 10 years following cessation of exposure, radiation-induced lung cancer risks were reduced to about half the level observed within 10 years of exposure. It is possible that cessation of smoking might have contributed to this reduction as well as to the reduction observed in ankylosing spondylitis patients.

None of the above studies can be regarded as providing conclusive evidence for the attenuation of relative risks with time from exposure, and this evidence does not seem strong enough to support a model in which risks are assumed to cease after some period of time. However, these data do support some modification of a model in which the large relative risks observed early in life remain constant for a lifetime. As discussed in Section 3.3.6 on age at exposure, assumptions regarding the persistence of relative risks are most critical for those exposed early in life.

The relative risk projection model has been used for central and upper estimates for most cancer sites (leukemia, bone, thyroid, and skin cancer are exceptions). Estimates based on the absolute risk projection model have also been provided, and are used as 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. The absolute and relative risk projection models lead to very similar estimates of the number of years of life lost (Table 2.2).

3.3.3 Projection of Risks Across Populations

In addition to extrapolating beyond the period for which follow-up data are available, it is 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). 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 3.4.

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 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 are much lower than the national average (Mason et al., 1975).

3.3.4 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 lifetime absolute risk incidence estimates, the ratio of the lifetime relative incidence and mortality estimates is multiplied by the lifetime absolute mortality estimate (see Section 3.7 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 lifetime relative risk mortality estimate, and to U.S. incidence rates to obtain a lifetime relative risk incidence estimate. To obtain an absolute mortality estimate, the ratio of these two relative 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 3.4.6.

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 percent. 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 to 1980 was 32 percent, and that for all childhood cancers (including leukemia) is 57 percent (National Cancer Institute, 1983). The survival rates vary by the type of leukemia and by the age at diagnosis. These improving survival 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 using the survival 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 5-year survival rate cannot necessarily be considered a cure rate.

Cure rates for cancers other than leukemia are also improving (National Cancer Institute, 1983). 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 3.3).

3.3.5 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 to 3 years and the excess shows a peak about 5 to 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. Because of 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 2 years for leukemia and bone cancer, 5 years for thyroid cancer, and 10 years for other cancer sites, choices that are supported by epidemiological data (BEIR III). In addition to the minimal 10-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.

3.3.6 Age at Exposure

Data from epidemiological studies indicate that radiation risks depend upon age at exposure. As can be seen from Tables 3.7.1 and 3.7.2 (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; Darby et al., 1987) 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.

It is, of course, the youngest age-at-exposure groups for whom the greatest projection of risks over time is required. A difficulty in allowing for the dependency of risks on age at exposure is that relatively few deaths have occurred in the youngest age-at-exposure groups, so that risks are imprecisely estimated. Especially large relative risks have been demonstrated in the youngest age groups, and the extrapolation of these large relative risks over a lifetime has a large impact on the estimated total population risk.

For breast and thyroid cancer, age-at-exposure-specific estimates have been obtained as described in Section 3.4.3 and 3.4.6. In the first edition of this report, single relative risk coefficient estimates, based on combined data from all exposure ages, were used to calculate the central and upper bound risk estimates for gastrointestinal cancer, lung cancer, and the category of other cancers. These estimates have been based primarily on atomic bomb survivor data. Since most of the cancer deaths occurred to those exposed over age 20, these estimates can be considered as most appropriate for those exposed in this age group; atomic bomb survivors exposed early in life are just beginning to experience substantial cancer risks.

Recently, the National Institutes of Health (1985) has formulated a model for cancer risks that includes a strong dependence of relative risks on age at exposure for nearly all cancers. In addition, recent analyses of the atomic bomb survivor data (Preston et al., 1987) have provided separate relative risk estimates for those under and over age 20 at exposure for several specific cancer types. For the combined category including all cancers except leukemia, the relative excess risk coefficient for those exposed under age 20 is 59 percent per Gy (90 percent confidence limits 39 to 80 percent), while that for those exposed over age 20 is 13 percent per Gy (90 percent confidence limits 8 to 18 percent). The coefficient based on combined data from both groups is 17 percent per Gy (90 percent confidence limits 13 to 21 percent). These estimates are based on tissue kerma dose with T65D dosimetry. Thus the relative excess risk coefficient for those exposed under age 20 is about three or four times the corresponding coefficient based on the entire study population. The comparable ratios for specific cancers appear to be reasonably consistent with this value.

Although the evidence is fairly clear that risks for those exposed early in life are larger than for those exposed later, the large confidence limits given above indicate considerable uncertainty in quantifying this

differential. There is also uncertainty in whether the large relative risks for those exposed at young ages will persist for a lifetime as discussed in Section 3.3.2. In calculating upper estimates for gastrointestinal cancers, lung cancer, and other cancers, the relative risk coefficients used in the first edition for those exposed under age 20 have been multiplied by three. The relative risk coefficients for these cancer categories for those exposed over age 20 have not been modified from those used in the first edition. This change has the effect of approximately doubling the estimated upper bound lifetime risks for the categories affected. Central estimates for gastrointestinal cancers, lung cancer, and other cancers have been based on the assumption that relative risks for those exposed under age 20 are the same as for those exposed later in life. The same approach was used in the first edition of this report. The treatment of age at exposure for estimates based on the absolute risk model has not been modified; that is, these estimates are based on a single absolute risk coefficient for all ages.

A model was also considered in which relative risks for those exposed under age 20 were assumed to be three times those used earlier, but only for the first 34 years of follow-up. After 35 years, it was assumed these risks had declined to the level used for those exposed at older ages. Since very little of the risk for those exposed early in life is expressed during the first 34 years, lifetime risks based on this approach were never increased more than 5 percent over those provided by the model used for central estimates. Although the allowance for age at exposure in this manner is in reasonable conformity with available data (especially data from the atomic bomb survivors), in practice this model provides estimates that are nearly identical to those based on the assumption of constant relative risks for all exposure ages. Age-specific risks for those exposed under age 20 are modified more than overall estimates using this alternative approach, but not more than about 10 percent.

It should be recognized that there is considerable uncertainty in choosing the appropriate model for age at exposure. Estimates of risks for those exposed under age 20 are statistically imprecise, and it is not known whether risks will continue to be expressed late in life, decades after the exposure has occurred, and when spontaneous risks are very much larger. The approach used here for obtaining upper bound estimates is reasonably consistent with that used in BEIR III and in the NIH Report (1985). The modification of this procedure for central estimates appears justified in light of recent data and analyses discussed in this section and in Section 3.3.2.

3.4 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 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 to 1978) of follow-up data since the publication of BEIR III.

3. The 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 3.2 and 3.3 and are discussed below. With the exception of breast cancer, the non-age-specific relative risk coefficients 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 3.6). The procedure is similar to that used in BEIR III except that the follow-up period has been extended by 4 years to account for the fact that the most recent data from the Japanese studies are included. The age-specific relative risk coefficients are obtained as described in Section 3.3.6.

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 3.2. Analogous estimates for incidence are presented in Table 3.3. These are upper bound linear risk estimates that must be modified as indicated in Section 3.3.1 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 3.7.

3.4.1 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 to 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 3.7). The use of the age- and gender-specific estimates (as in BEIR III) yields similar risk estimates.

3.4.2 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 to 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 death per 10^4 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 that for 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 to 5 deaths per 10^4 per Gy are suggested for the present report, which would correspond to annual risks of 0.08 to 0.20 deaths per 10^4 PY per Sv, given by UNSCEAR, if a 25-year expression period is assumed.

3.4.3 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 to 19 years at exposure and 6.6 cases per 10^4 WY per Gy for

women aged ≥20 years at exposure, while the respective relative risk estimates for these two groups are 103 percent per Gy and 42 percent per Gy. These estimates are based on the assumption of a latent period of 20 years for women aged 10 to 14 at exposure, of 15 years for women aged 15 to 19 at exposure, and 10 years for women aged ≥20 at exposure.

Age-at-exposure-specific risk estimates for the Japanese atomic bomb survivors (Land et al., 1980) and 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 recent Japanese data indicate that females exposed under age 10 are showing an excess of breast cancer (Tokunaga et al., 1982).

Since the BEIR III risk estimates (obtained from U.S. data) for those aged 10 to 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 to 19 and the ≥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 percent per Gy. For the central and lower bound estimates, these coefficients 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 to 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 was applied 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 3.1, and lifetime incidence estimates based on the procedures described above, using both relative and absolute projection models, are presented in Table 3.3. Mortality estimates, which are presented in Table 3.2, are obtained as described in Section 3.3.4 and in Section 3.7.

3.4.4 Lung Cancer

Because a portion of the exposure received in a nuclear power plant accident might 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 3.8. 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 ages 10 to 19, has been calculated by Kato and Schull 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.

Table 3.8

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 (1982)
[b]Wakabayashi et al. (1983)
[c]Smith and Doll (1982)
[d]An RBE of 10 is assumed. See text for complete explanation.

When absolute risks for lung cancer are examined by age at exposure and age at death (Table 3.7), 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 percent per Gy, about half the relative risk coefficient of 37 percent 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 double those in Japan.

Although the value 18 percent is somewhat closer to that obtained from the British ankylosing spondylitis patients (25 percent), and although the comparison of breast cancer risks in Japan and the U.S. discussed in Section 3.4.3 would also support the use of this value (18 percent), 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 percent) is more appropriate, while a multiplicative model would support using the value of 37 percent 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 percent has been used for the central estimate. For the upper bound, the coefficient 37 percent has been used for those exposed over age 20, while 3 times this value (111 percent) is used for those exposed under age 20. The absolute risk projection model is used to obtain the lower bound. The linear mortality estimates based on these models are presented in Table 3.2. 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 percent (67 deaths per 10^4 per Gy), but smaller than the upper bound estimate (245 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 sufficient detail in a way that examines both age at exposure and age during the follow-up period. Estimates of the relative risk coefficient based on mining populations range from 1.8 percent per WLM (working level month), calculated from data on Czechoslovakian miners (BEIR III), to 0.31 percent (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 percent and 0.31 percent per WLM) correspond to 26 percent per Sv and 4 percent per Sv, respectively. These estimates are reasonably comparable with those based directly on low-LET exposure.

3.4.5 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 3.9. There is considerable uncertainty in the estimates, and it is difficult to reconcile the discrepancy between the Japanese Life Span Study and the Nagasaki 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 3.9 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:

Table 3.9

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	Study: Nagasaki Tumor Registry[b]	Study: 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)	0.74[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 pancreas, 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 estimates 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).

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 percent 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 to 2.8 deaths per 10^4 PY per Gy. Finally, data on cervical cancer patients provide no evidence of an association between 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 to 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 percent per Gy. This value is considerably larger than the relative risk of 12 percent per Gy (Land, 1983), based on the Life Span Study, and slightly larger than the relative risk of 33 percent 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 percent per Gy for calculating non-age-specific risks. For age-specific risks, the coefficients 117 percent and 39 percent have been used for those exposed under and over age 20, respectively. Lifetime risk estimates based on the linear model are presented in Tables 3.2 and 3.3.

3.4.6 Thyroid Cancer and Benign Thyroid Nodules

The linear risk coefficients for thyroid cancer and for benign thyroid nodules are those presented in 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 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. 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 3.2 and 3.3 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 percent 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 3.2), this overestimation does not represent a serious problem.

3.4.7 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 since the data are limited.

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 degrees) 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 percent 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 3.4. 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 10-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.

3.4.8 Other Cancers

Determination of risks from the residual of cancers that are not included in the categories noted above is very difficult. There may be types of cancer that have not been specifically linked with radiation simply because they are too rare or not precisely enough diagnosed to have been studied adequately. On the other hand, if only cancer types showing positive correlations are selected, while those showing negative correlations are omitted from consideration, overestimation of risks can result.

Cancers, other than those described in the previous sections, for which there is reasonably good evidence of an association with radiation, include multiple myeloma, and cancers of the urinary bladder, kidney, and brain. Evidence of an association for lymphoma and for cancers of the 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 0.85 cases per 10^4 PY per Gy for urinary cancer, 0.27 cases per 10^4 PY per Gy for lymphoma, and a residual estimate of 1.0 cases per 10^4 PY per Gy. Mortality estimates would of course be somewhat lower. However, more recent data do not support the association originally identified for lymphoma (Miller and Beebe, 1986).

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 are not adequate to investigate the adequacy of the relative risk model or the effect of age at exposure.

In order to calculate an appropriate dose for this group, the proportions of specific cancers comprising the group are needed. This is extremely difficult to determine, because for most of the cancers in this group available estimates are very imprecise and vary widely from study to study. In addition, cancers that have not been specifically linked with radiation simply because of inadequate data may comprise a substantial proportion of the "other cancer" group. It is suggested that doses to the bone marrow, kidney, urinary bladder, brain, uterus, and ovary be considered in making the dose calculation. If some of these organ-specific doses cannot be obtained, using an average of those that are

available is a reasonable solution given the general uncertainty regarding the exact mix of cancers comprising this group.

3.4.9 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 yielding a total lifetime risk of 580 deaths per 10^4 per Gy for those exposed in utero. 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) have noted that this finding is inconsistent with the risk 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 72 provided an estimate of 230 deaths per 10^4 population in utero per Gy for leukemia and other fatal cancers combined, a reduction by a factor of 2.5 over the comparable value of 580 from BEIR III. The estimate of 230 was not modified in either the 1977 or the 1986 UNSCEAR reports. UNSCEAR 86 provides a thorough discussion of the recent literature on cancers resulting from in utero exposure. We have used the UNSCEAR values for the central estimates and lower bounds for cancers due to in utero exposure. 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.

3.4.10 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 3.2, with that obtained directly from the Japanese Life Span Study.

The absolute linear risk coefficient for the period 1955 to 1978 based on average organ dose and an RBE of 10 for neutrons 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 to 33 years after follow-up, is 23 percent 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 non-age-specific lifetime risk estimates for all cancers other than leukemia and bone presented in Table 3.2. 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.

3.5 Comparison with Reactor Safety Study Model for Latent Somatic Effects

Since the publication of the Reactor Safety Study (Nuclear Regulatory Commission, 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, age-at-exposure-specific estimates have been used in calculating upper estimates for most cancer types. Fourth, more recent epidemiological data has been considered in determining numerical risk coefficients. Fifth, 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. Sixth, 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).

Seventh, 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.

3.6 Use of the Model for Estimating Risks for Specific Groups Defined by Sex and Age at Exposure

The model for estimating cancer risks has been designed for the estimation of risks resulting from exposure to a population similar in age and sex composition to that of the United States in 1978. Although in general the model is not adequate for estimating risks for individuals or groups with specific characteristics, reasonably valid estimates can be obtained for certain broad subgroups of persons. In particular, those under age 20 and those over age 20 have been considered separately in developing the models used in this report. Thus separate estimates for these age-at-exposure groups are appropriate. Since the experience of persons exposed over age 65 has contributed very little to the determination of the risk coefficients used in this report, estimates for the over-age-20-at-exposure group can be considered reasonably appropriate for an occupational group exposed between the ages of 20 and 65.

For leukemia, thyroid cancer, and breast cancer, there is clear evidence that risks differ by sex. For leukemia, there is evidence that absolute risks are larger for males than for females, and risk coefficients presented in BEIR III for males are about 1.5 times those for females. It is suggested that the overall risks for a population composed of both sexes be multiplied by the factor 1.2 to obtain risks for a male population, and by the factor 0.8 to obtain risks for a female population. For thyroid cancer, risks for females appear to be larger than risks for males, and in this case it is suggested that the overall risks for a population composed of both sexes be multiplied by the factor 0.667 to obtain risks for a male population, and by the factor 1.333 to obtain risks for a female population. These are the factors suggested in Table A.3 of Appendix A. Risk of radiation-induced breast cancer has been demonstrated only in females, and the population-based risks (as given in Table 3.0, for example) have been obtained by dividing the risks for females by two. Thus, to obtain estimates for females alone, these values must be multiplied by two, while the risk for males alone would be zero.

Evidence for possible modification of risks by sex is not so clear for cancers other than those noted above. Recent analyses of the atomic bomb survivor Life Span Study (Preston et al., 1987) demonstrate that for most cancers, absolute risks are fairly comparable for males and females, while relative risks are not always comparable, especially for sites (such as lung cancer) where spontaneous risks differ substantially for the two sexes. This suggests that lifetime risks for males and females

should be similar. However, because more females live to ages when cancer rates are high, female risks will tend to be slightly higher than risks for males.

One approach to sex-specific risk estimation is to assume that absolute risk coefficients are the same for the two sexes, and to use the approach described in Section 3.3.3 (Projection of Risks Across Populations) to obtain sex-specific relative risk coefficients. These relative risk coefficients can then be applied to sex-specific U.S. rates, using sex-specific life tables (see appendix) to obtain sex-specific lifetime risks. Using this approach, factors by which overall risks are to be multiplied to obtain male and female risk estimates can be obtained. Factors obtained in this manner are presented in the table below. These factors are appropriate for risks expressed as the number of cancer deaths per 10^4 per Gy.

	Absolute Risk Projection Model		Relative Risk Projection Model	
Cancer	Males	Females	Males	Females
Lung	0.92	1.08	0.91	1.08
Gastrointestinal	0.94	1.06	0.86	1.13
Other	0.94	1.06	0.92	1.08

Risks for females are slightly larger than those for males, primarily because of their longer life expectancy. There is considerable uncertainty in these factors since the assumption of equal absolute risk coefficients may not be correct. If, for example, we assumed equal relative risk coefficients for lung cancer risks in males and females, lifetime risks would be much smaller for females than for males. This latter assumption does not seem consistent with the atomic bomb survivor data, but would be reasonable if radiation and smoking were assumed to interact multiplicatively.

Thus, if sex-specific estimates are desired, it is suggested that risks for lung cancer, gastrointestinal cancers, skin cancer, and other cancers be considered equal for the two sexes. It is possible to allow for the longer life-span for females by applying the factors in the above table, but given the general uncertainty regarding the comparability of risks for the two sexes, this refinement does not seem warranted.

3.7 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 3.3.1. 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 where k > j. Then $y_{jk} = 5\left[\frac{{}_5L_{5k}}{{}_5L_{5j}}\right]$ 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 Part I, Table A.2). Let A indicate the absolute risk expressed as excess cancer deaths (or 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 1978 U.S. mortality data (see Part I Table A.3) for the cause of death being evaluated. Incidence rates are given in Part I, Table A.4.

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

$$P = \sum_j f_j \left[0.5\, y_{j,j+2} + \sum_{k=j+3}^{18} y_{j,k}\right] \qquad (3.1)$$

(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 (or cases) per 10^4 population per Gy that would result from an effect of 1.0 death (or case) per 10^4 PY per Gy. The mean number of years of life lost following a death can be estimated by the ratio

$$Q = \frac{1}{P} \sum_j f_j \left[0.5\, y_{j,j+2}\, \frac{\mathring{e}_{j+2} + \mathring{e}_{j+3}}{2} + \sum_{k=j+3}^{18} y_{j,k}\, \frac{\mathring{e}_k + \mathring{e}_{k+1}}{2}\right] \qquad (3.2)$$

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 $(\mathring{e}_k + \mathring{e}_{k+1})/2$ 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 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 persons 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 x 33.66 = 90.87 deaths per 10^4 per Gy and 90.87 x 24.46 = 2223 years of life lost per 10^4 per Gy. In Table 3.10, 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 3.11. Values of P based on female life tables and the age distribution of females are also presented and are used for breast cancer calculations.

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 to 33.5 years of follow-up), we would have:

$$r = A \sum_j g_j \left[0.6\, y_{j,j+2} + \sum_{k=j+3}^{j+6} y_{j,k} + 0.2\, y_{j,j+7} \right]$$

and

$$s = \sum_j g_j \left[0.6\, y_{j,j+2}\, \lambda_{j+2} + \sum_{k=j+3}^{j+6} y_{j,k}\, \lambda_{j,k} + 0.2\, y_{j,j+6}\, \lambda_{j+7} \right]$$

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 to 9 years at exposure, 0.215 for 10 to 19 years, 0.199 for 20 to 34 years,

Table 3.10

Deaths per 10^4 Population and Their Distribution by Age at Exposure

	Age at Exposure (yrs)					
	0-9	10-19	20-29	30-39	≥40	Total
Proportion of population in age group[b]						
Both Sexes	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						
Deaths occurring 10+ years following exposure	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 2-17 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	56.78	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 from 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 the 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 3.11

Years of Life Lost Per Death by Age at Exposure[a]

Model	Age at Exposure (yrs) 0-9	10-19	20-29	30-39	≥40	All Ages[d]
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 are excluded.

[d]From population with U.S. age structure (1978), and assuming the same risk coefficient for all exposure ages.

0.233 for 35 to 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

$$S = \sum_j f_j \left[0.5\ \lambda_{j+2}\ y_{j,j+2} + \sum_{k=j+3} \lambda_k\ y_{j,k}\right] \qquad (3.3)$$

The mean number of years lost following a death is given by

$$T = \frac{1}{S} \sum_j f_j \left[0.5\ \lambda_{j+2}\ y_{j,j+2}\ \frac{\mathring{e}_{j+2} + \mathring{e}_{j+3}}{2} + \sum_{k=j+3} \lambda_k\ y_{j,k}\ \frac{\mathring{e}_k + \mathring{e}_{k+1}}{2}\right] \qquad (3.4)$$

The expressions given in equations (3.3) and (3.4) have been evaluated for four major cancer categories with the results given in Tables 3.10 and 3.11, 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 percent per Gy are 0.39 x 484.6 = 189.00 deaths per 10^4 per Gy and 189.00 x 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 3.10 and 3.11, 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% x 104.8) + (42% x 162.3) = 175 deaths per 10^4 per Gy. With the exception of breast cancer, calculations provided in this report are not gender-specific. The estimation of risks for specific groups defined by gender and age at exposure is discussed in Section 3.6.

Other latent periods and risks assumed to persist for less than a lifetime can be obtained by modifying equations (3.1)-(3.4) 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 3.10 and 3.11.

Incidence estimates using the relative risk model can be obtained by substituting incidence rates for mortality rates λ_k in expression (3.3). 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 (3.4) with incidence rates and then subtracting the corresponding number of years of life lost. Tables 3.12 and 3.13 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 percent per Gy, by the number of spontaneous cases given in Table 3.12, 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 3.2. The years of life lived after cancer occurrence for the relative risk model is obtained as 322.1 x 5.34 (from Table 3.13) = 1720. For the absolute risk model the number of years of life lived after cancer occurrence is (154.87 90.87) x 24.46 (from Table 3.11) = 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 computations did not seem necessary.[1] 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.

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[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 percent 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 percent. Even in the more extreme situation of a population exposed to 1 Gy, such adjustment decreased the lifetime risk estimate only by about 10 percent, a fairly small amount relative to other uncertainties.

Table 3.12

Spontaneous Cancer Cases Per 10^4 Population and Their Distribution by Age at Exposure[a,b]

Cancer Type	Age at Exposure (yrs) 0-9	10-19	20-29	30-39	≥40	Total
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 3.13

Years of Life Lived After Cancer Diagnosis Per Case by Age at Exposure Under Relative Risk Projection Model[a]

Cancer Type	Age at Exposure (yrs) 0-9	10-19	20-29	30-39	≥40	All Ages[d]
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), and assuming the same risk coefficient for all exposure ages.

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. Moreover, 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 3.10-3.13.

3.8 References

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APPENDIX 3A

Example Calculations

Appendix 3A

To illustrate the application of the formulae in Section 3.7, we show the details in calculating the quantities in expressions (3.1), (3.2), (3.3), and (3.4) 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 ${}_5L_{5k}$, $y_{j,k} = 5 \bullet \left[\frac{{}_5L_{5k}}{{}_5L_{5j}}\right]$, $\mathring{e}_k$, $\frac{\mathring{e}_k + \mathring{e}_{k+1}}{2}$, λ_k (for cancers of the digestive system) are shown in Table 3A.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 (3.1): The term for j=4 (age 20-24) is given by

$$f_4\left[0.5\ y_{4,6} + \sum_{k=7} y_{4,k}\right]$$

= 0.093 [0.5 x 4.93 + 4.89 + . . . + 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 3.10. (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 (3.2): The term for j=4 in the numerator of this expression is given by

$$f_4\left[0.5\ y_{4,6}\ \frac{\mathring{e}_6 + \mathring{e}_7}{2} + \sum_{k=7} y_{4,k}\ \frac{\mathring{e}_k + \mathring{e}_{k+1}}{2}\right]$$

= 0.093 [0.5 x 4.93 x 43.4 + 4.89 x 38.7 + . . . + 0.13 x 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 3.11. The years of life lost per death for all ages is obtained by summing the terms in the numerator of (3.2) across all exposure ages and dividing by 33.66, the value for expression (3.1).

Expression (3.3): The term for j=4 is given by

$$f_4\left[0.5\ \lambda_6\ y_{4,6} + \sum_{k=7} \lambda_k\ y_{4,k}\right]$$

which equals 0.093 (545.5) = 50.73 while the term for j=5 equals 0.082 (547.3) = 44.88. The sum is given by 95.61, the value found for age 20-29 under gastrointestinal cancers in Table 3.10.

Table 3A.1

Data Needed for Illustrative Lifetime Risk Calculations

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}	Years Lived in the Interval by Persons Alive at the Beginning of: the 5th Interval Y_{5k}	Life Expectancy at Beginning of Interval $\overset{\circ}{e}_k$	Average Life Expectancy in Interval $\frac{\overset{\circ}{e}_k + \overset{\circ}{e}_{k+1}}{2}$	Baseline Risk λ_k[b]
0	0	492,652	--	--	73.3	71.4	0.02
1	5	491,312	--	--	69.5	67.1	0.01
2	10	490,573	--	--	64.6	62.2	0.01
3	15	488,960	--	--	59.7	57.4	0.02
4	20	485,985	--	--	55.0	52.7	0.04
5	25	482,735	4.96655	--	50.4	48.1	0.10
6	30	479,538	4.93366	4.96689	45.7	43.4	0.24
7	35	475,679	4.89395	4.92692	41.0	38.7	0.52
8	40	470,041	4.83595	4.96852	36.4	34.2	1.18
9	45	461,238	4.74538	4.77734	31.9	29.8	2.50
10	50	447,647	4.60555	4.63657	27.6	25.6	4.31
11	55	427,499	4.39826	4.42789	23.5	21.6	7.91
12	60	398,024	4.09402	4.12259	19.7	18.0	13.31
13	65	358,257	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) S1-1104, Hyattsville, MD, 1980.

[b]Risk per 10,000. See Table A.3 "1978 Mortality Rates per 100,000 Population" Gastrointestinal Cancer in Appendix A of Part I: Introduction, Integration and Summary.

Expression (3.4): The term in the numerator for j=4 is given by

$$f_4\left[0.5\ \lambda_6\ y_{4,6}\ \frac{\mathring{e}_6 + \mathring{e}_7}{2} + \sum_{k=7} \lambda_k\ y_{4,k}\ \frac{\mathring{e}_k + \mathring{e}_{k+1}}{2}\right]$$

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 3.11 for the 20-29 age group for gastrointestinal cancers.

4.0 GENETIC EFFECTS

S. Abrahamson, University of Wisconsin
M. A. Bender, Brookhaven National Laboratory
C. Denniston, University of Wisconsin
W. J. Schull, University of Texas

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 percent 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). For low-LET radiation 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. In order to produce that number

of births there would have been a minimum of 740,000 conceptions required since it is believed that about 35 percent (260,000) of all conceptions lead to spontaneous periimplantation loss (losses that occur mostly within the first eight weeks after conception). 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 familial 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. About 230 additional conceptions would have been required to replace the same number of cases of periimplantation loss resulting from both inviable aneuploidy and unbalanced translocations at this exposure level. The dominant and X-linked disorders will be selected against but will persist on average for 5 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 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 of genetic diseases 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.[1] 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 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

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[1]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 generations.

(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 x 33 years of life lost per case) since the most severe cases would not reproduce beyond the first generation. The committee has not attempted to introduce the concept of years of life lost for either the cases of spontaneous or induced periimplantation wastage. This concept of years of life lost is an attempt to measure severity of disease. The committee feels it is inappropriate to put a severity value on unrecognized conceptions either spontaneous or induced.

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 an 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 percent 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.

4.1 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, 1982). 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, 1982). The recently released BEIR IV report (NAS, 1988) provides RBE values for genetic effects from incorporated plutonium--2.5 for mutations and 15 for chromosomal aberrations.

It has been estimated that about 50 percent 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.

4.2 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 4.1, and a tabular listing of the major representative diseases in each class is presented in Appendix 4E. The listing is taken from the UNSCEAR Reports of 1977 and 1982.

The BEIR III committee (NAS, 1982) estimated that 10.7 percent 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, 1982) 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 4A for further discussion).

4.3 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 is on the other X chromosome. We emphasize here that for newly occurring sex-linked mutations

Table 4.1

Numbers of Naturally Occurring and Radiation-Induced Genetic Disorders in a Population of One Million, According 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] First Generation[c]	BEIR III Report[b] All Generations[d]	This Study (central estimates) First Generation[c]	This Study (central estimates) All Generations
Single-gene	4,800	3-30	20-100		
Autosomal Dominant				15[e]	70
X-Linked				4	20
Irregularly Inherited	43,200	-	10-400	-[e]	70[f]
Chromosome Aberrations[g]	2,880	<5	5		
Aneuploidy				4	5
Unbalanced Translocations				6	8
TOTALS[h]	50,900	-	-	30	175
Periimplantation Wastage	260,000	-	-	230	240

[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]Estimated directly from measured phenotypic damage or from observed cytogenic effects.

[d]Based on doubling dose of 0.50-2.50 Gy, chronically delivered. Actually 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.

[e]First generation of irregularly inherited incidence included within first generation of single-gene incidence.

[f]Based on doubling dose of 1 Gy and 10 generations mean persistence time, which is very uncertain.

[g]Includes only aberrations expressed as congenital malformations resulting from unbalanced translocations, 480; and from aneuploidy (numerical aberrations), 2,400; equilibrium time 1-2 generations and 1 generation, respectively.

[h]Totals rounded off to avoid perception of false precision.

only those arising in female gametes will be immediately manifest in the male offspring. For those arising in male gametes the affected mutant male offspring will only be apparent in the second generation, i.e., in the grandsons of the male parent transmitting the new X-linked mutation. Of all liveborn, 1 percent 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 percent 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. 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, 1982, and UNSCEAR, 1982). In Appendix 4C, 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 percent of all liveborn. However there is considerable uncertainty in this 9 percent value, depending upon which

diseases are included in the analysis. The value of 9 percent 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 percent 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.

Both numerical changes and structural chromosome rearrangements more often lead to fertilized eggs that are either incapable of implantation or are incapable of normal development shortly after implantation. We refer to these cases as periimplantation wastage since they usually occur well within the first 8 weeks after conception and most often such pregnancies go unrecognized. At present it has been estimated that about 35 percent of all conceptions are spontaneously lost in this period with perhaps an additional 10 to 15 percent contributing to a class of recognized abortions (see discussion in UNSCEAR, 1982, p. 432). This means, of course, that somewhere between 1,500,000 and 2,000,000 conceptions are normally required to produce 1,000,000 liveborn individuals.

4.4 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.

4.4.1 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 percent 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 4B). 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 x 10^{-4}/Gy (central estimate; see Appendix 4D for the range). Essentially the method of calculation of risk can be summarized in the following equation:[2]

$$\text{RISK} = \underset{\text{(A)}}{\begin{bmatrix}\text{Induction}\\ \text{rate of}\\ \text{skeletal}\\ \text{mutants}\end{bmatrix}} \bullet \underset{\text{(B)}}{\begin{bmatrix}\text{Correction}\\ \text{for dose}\\ \text{dose rate,}\\ \text{and frac-}\\ \text{tionation}\end{bmatrix}} \bullet \underset{\text{(C)}}{\begin{bmatrix}\text{Correction}\\ \text{for total}\\ \text{dominant}\\ \text{diseases}\end{bmatrix}} \bullet \underset{\text{(D)}}{\begin{bmatrix}\text{Correction}\\ \text{for serious-}\\ \text{ness}\end{bmatrix}} \bullet \underset{\text{(E)}}{\begin{bmatrix}\text{Correction}\\ \text{for sex}\end{bmatrix}} \qquad (4.1)$$

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 to 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

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[2]Where in the experiment of Selby and Selby (1977) (A) = 37 observed skeletal mutants in 2,646 female offspring; (B) = 1/6 extrapolation from 6 Gy to 1 Gy on a linear model, the correction of 1/3 is for dose rate reduction and the factor 1/1.9 is used to adjust for the effectiveness factor of a fractionated 5 Gy + 1 Gy exposure with 24-hour intervals. (Such an exposure was 1.9 times as effective in this experiment as a single 6-Gy exposure.) Skeletal diseases are believed to constitute in the range of 1/5 to 1/15 of all human genetic disorders, thus the factor (C) and where (D) represents the estimate 0.25 to 0.75 of these skeletal disorders that would represent serious genetic disabilities. The term (E) employing a factor of 1 suggests that the male and female germ cells of import are at the same sensitivity to radiation. These are the factors used by BEIR III, although the value of (E) was different.

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 4C). 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 4C 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. It should be noted that their higher doubling dose estimates would lead to an even smaller number (about 400) of first generation cases.

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 percent 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 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). We have assumed (as has UNSCEAR, 1977) an average persistence time of five generations for newly introduced X-linked mutations, as was done for dominant mutations. This implies that the viability or probability of survival to reproduction is 80 percent of a normal male. (Again we note these facts for those attempting to follow our calculations. When a population is exposed to irradiation, their first generation male offspring affected with newly induced sex-linked disorders would have inherited their disorders exclusively from their

mothers. The mutations induced in the paternal gametes will not be observed until the second generation of males appear. The affected second generation males will have inherited their X-chromosomes from their mothers who could have received the mutant X-chromosome from either of their irradiated parents.)

4.4.2 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:

$$\text{Risk} = (\text{incidence})(\text{relative mutation risk})(\text{mutational component}) \quad (4.2)$$

The relative mutation risk is taken as 1 because the doubling dose is 1 Gy. BEIR III used a relative mutation risk of 1/100 for a 1-rad exposure. 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 x 1 x 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 x 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 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.

4.4.3 Chromosome Aberrations

4.4.3.1 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 x 10^{-2}. After correction for dose and dose rate (0.1 to 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 ((1980) Trunka, personal communication) of aneuploid offspring produced by translocation carrier parents suggests that the 5 percent 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 to 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 4.5.1), 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

$$7.4 \times 10^{-2} \times (1/2) \times (1/2.5) = 1.48 \times 10^{-2}/\text{Gy} \qquad (4.3)$$

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:

$$1.48 \times 10^{-2} \times 1/4 = 3.7 \times 10^{-3}/\text{Gy}$$

(Balanced Translocations from Males) (4.4)

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:

$$1.48 \times 10^{-2} \times (1/2) \times (1/10) = 7.4 \times 10^{-4}/\text{Gy}$$

(Unbalanced Translocations from Males) (4.5)

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[3]See NCRP 1980 for RBE of cobalt-60 γ-rays vs 250 kVp x-rays.

Similarly, the estimate of the induced frequency of periimplantation loss, i.e., zygotic deaths occurring mainly within the first eight weeks post conception, is therefore: $1.48 \times 10^{-2} \times (1/2) \times (9/10) = 6.7 \times 10^{-3}$/Gy, the inviable unbalanced translocation products from male irradiation. (In Appendix 4D this number has been rounded off to 7.0×10^{-3}/Gy.)

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,

$$(1.48 \times 10^{-2})(1/16) = 9.25 \times 10^{-4}/\text{Gy} \qquad (4.6)$$

for balanced translocations.

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,

$$(1.48 \times 10^{-2})(6/16)(1/10) = 5.6 \times 10^{-4}/\text{Gy} \qquad (4.7)$$

for unbalanced translocations.

Correspondingly, for irradiated females the periimplantation wastage estimate is $1.48 \times 10^{-2} \times (6/16) \times (9/10) = 5.0 \times 10^{-3}$/Gy. Thus we would expect in the next generation about 1,300 cases of viable unbalanced diseases 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. The second generation would be expected to produce about 25 percent of this number of cases with a 50 percent reduction in each successive generation.

4.4.3.2 Aneuploidy

The 1980 BEIR III committee refrained from developing a risk estimate for

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[4]The oocyte will contain the reciprocal translocation distributed between two tetrads of chromatids. The probability of recovering a balanced translocation is 1/4 x 1/4 or 1/16, the probability of recovering normal products is 3/4 x 3/4 or 9/16, and the probability of recovering an unbalanced product is 2 x 3/4 x 1/4 or 6/16.

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, we recommend 500 cases/10^6 gametes/Gy. We will also assume that the yield of these aberrations follows a linear relationship throughout the anticipated dose-response curve.

Studies of Speed and Chandley reported in UNSCEAR (1982) indicate that mouse spermatogonia irradiated at 1 Gy produced about a 1.8 percent increase above controls in aneuploid implants as measured by cytological preparations carried out 9 to 10 days into gestation. These cases, as in the controls, consist of trisomies, triploids, monosomies, and mosaics. We shall assume then that this value 1.8 x 10^{-2}/Gy is the induced central value for male or female gametes with respect to periimplantation wastage. There is no transmissibility for these cases to subsequent generations as there is for the unbalanced translocation component of implantation loss.

4.4.4 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 4.1 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, 1982). 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 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 4.1 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

[5]The ICRP Task Group assumed the relative mutation risk for aneuploidy was the same as that for mutation (1 Gy).

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 percent and the unbalanced chromosome anomalies by about 33 percent. Chromosome anomalies are expected to have a three generation average persistence, thus the reduction by 33 percent. 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 4.1.

4.5 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.

4.5.1 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:

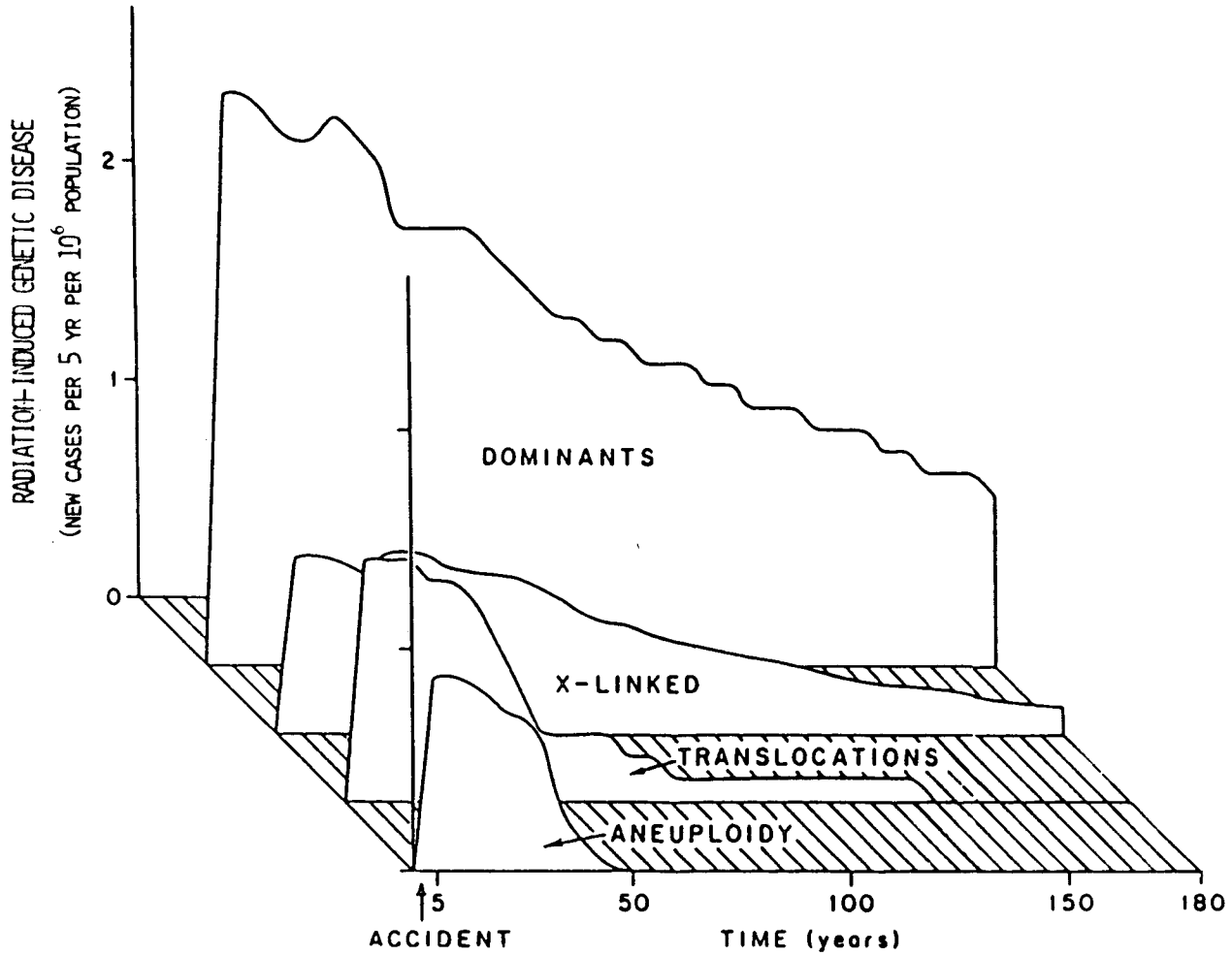

Figure 4.1. Incidence of Radiation-Induced Genetic Disorders. Effect of a uniform gonadal dose of 0.01 Gy, delivered acutely.

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 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 $\alpha_D/\alpha_r \simeq 90$ (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:

$$Y = (1.5 \times 10^{-3})d + (1.5 \times 10^{-3})d^2 \qquad (4.8)$$

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:

$$Y = (1.8 \times 10^{-3})d + (1.8 \times 10^{-3})d^2 \qquad (4.9)$$

per male or female gamete.

4.5.2 Chromosome Aberrations

4.5.2.1 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:

$$Y = (1.48 \times 10^{-2})d + (1.48 \times 10^{-2})d^2 \qquad (4.10)$$

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.

4.5.2.2 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:

$$Y_{\text{aneuploids}} = (5.0 \times 10^{-4})d \qquad (4.11)$$

4.6 Estimated Impact of Genetic Disease (Years of Life Lost)

Tables 46 to 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 percent impairment. X-linked disorders were estimated to cause 40 years of impaired life at about 40 percent 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 x 21) per million liveborn; for X-linked about 400 years (9 x 44); and for all chromosome anomalies about 1,370 years (10 x 46 + 13 x 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 percent to 30 percent. 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 x 0.48 or 68 cases throughout all times. These estimates scaled to the 1978 vital statistics are presented in Table 4.2. The resulting estimates can be compared with those resulting from the normal incidence of genetic disease.

4.7 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 5-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 4.3 and 4.4 and Figures 4.2 and 4.3 provide the summarized data for these two scenarios over the first five generations. In Appendix 4G we provide a description of the demographic assumptions

Table 4.2

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 4.1[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]	3,000	108,000			
Autosomal Dominant			10	300	1,500
X-Linked			6	180	900
Irregularly[f] Inherited	52,700	1,580,000	-	-	2,350
Chromosome[g] Aberrations					
Aneuploidy	3,700	110,400	6	180	230
Unbalanced Translocations	1,100	32,200	14	420	600
TOTALS[h]	61,100	1,830,000	40	1,100	5,600

[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 percent impairment = 21.

[e]Sex-linked estimate: 28 years lost + 40 years impaired life x 40 percent impairment = 44.

[f]Irregularly inherited disorders estimate: 30 years lost + 20 years impaired x 25 percent 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 4.3

Central Estimates of Radiation-Induced Genetic Effects, Scenario 1 (Chronic Exposure)[a,b]

Type of Disorder	Total Cumulative Cases: Years Since Accident				
	30[c]	60[c]	90[c]	120[c]	150[c]
Dominant[d]	110	240	360	440	510
X-Linked[d]	35	80	120	140	160
Aneuploidy	30	50	50	50	50
Unbalanced Translocations	45	80	100	100	100
Cumulative Mutant Totals	220	456	642	730	825
Cumulative Births	490,000	958,000	1,410,000	1,850,000	2,270,000
Periimplantation Wastage	1,500	2,500	2,700	2,700	2,750
Unbalanced Translocations	405	720	900	900	945
Aneuploidy	1,080	1,800	1,800	1,800	1,800

[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]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.

[c]Demography: 1978 projection (adjusted to produce stable population size).

Time Period (Yr)	Projected Birthrate (Birth/Yr)
0-29	16,000
30-59	15,600
60-89	15,000
90-119	14,700
120-149	14,000

[d]Assumes 80 percent viability of induced mutants in each generation.

Table 4.4

Central Estimates of Radiation-Induced Genetic Effects, Scenario 2 (Acute Exposure)[a,b]

Type of Disorder	Total Cumulative Cases: Years Since Accident				
	30[c]	60[c]	90[c]	120[c]	150[c]
Dominant[d]	8,960	16,330	22,180	26,850	30,570
X-Linked[d]	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	5,580	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
Periimplantation Wastage	65,900	81,450	86,600	88,800	89,700
Unbalanced Translocations	32,760	45,090	50,220	52,470	53,370
Aneuploidy	33,120	36,360	36,360	36,360	36,360

[a]Dose: 2 Gy in first interval, none in the following intervals.

[b]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.

[c]Demography: 1978 projection (adjusted to produce stable population size).

Time Period (Yr)	Projected Birthrate (Birth/Yr)
0-29	16,000
30-59	15,600
60-89	15,000
90-119	14,700
120-149	14,000

[d]Assumes 80 percent viability of induced mutants in each generation.

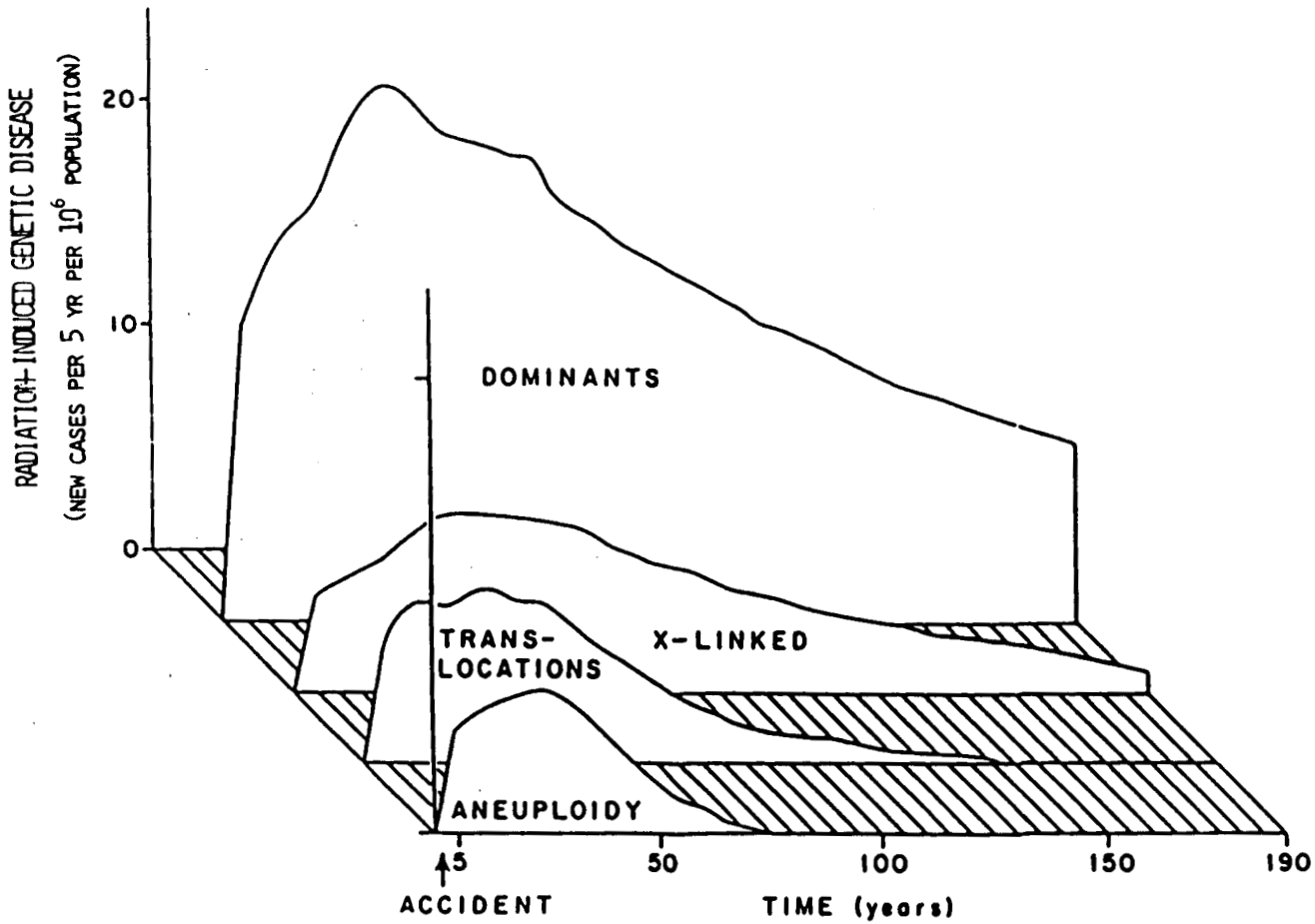

Figure 4.2. Incidence of Radiation-Induced Genetic Disorders. Effect of a uniform gonadal dose of 0.10 Gy, delivered chronically.

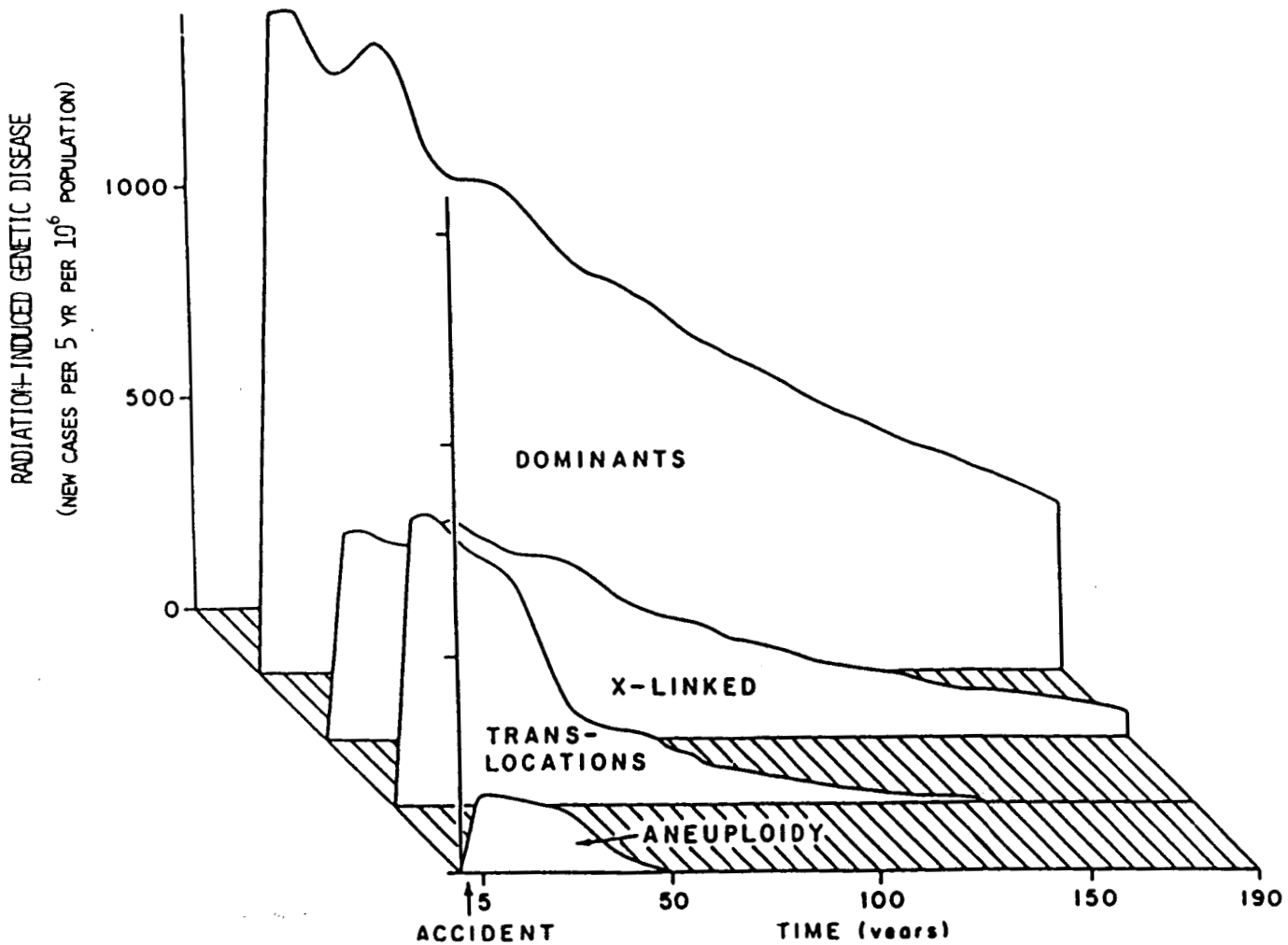

Figure 4.3. Incidence of Radiation-Induced Genetic Disorders. Effect of a uniform gonadal dose of 2.00 Gy, delivered acutely.

and programs utilized as well as a sample program output. (Copies of programs for the modelled genetic effects are available upon request.)

4.8 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 gonadal 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 4.5). We have used an average dose for each exposure group, that is 0.05 Gy (0.01 to 0.09 Gy parents groups), 0.295 Gy (0.10 to 0.49 Gy groups), 0.745 Gy (0.50 to 0.99 Gy groups) and 2.00 Gy ($\geq$ 1.00 Gy groups) and introduced these values into the equations presented in Section 4.5 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 parents. For example there were 1,040 deaths in this group of 16,713 progeny up to the age of 17 (6.22 percent). In the unexposed groups there were 2,191 deaths of 33,976 progeny produced (6.45 percent), 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

Table 4.5

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) 0.034	0.218	0.706	2.435	Total Estimated Number of Cases	Exposure Only[e]
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 3 cases and an upper bound estimate of 63 cases.

our calculations provide a not unreasonable estimate of the genetic effects observed in Japan.

4.9 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 x [10^{-4} d_1 + 10^{-4} d_1^2] where d_1 = 0.75 Gy) + (5000 people x [10^{-4} d_2 + 10^{-4} d_2^2] where d_2 is 1 Gy) etc.

4.10 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.

4.11 References

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Appendix 4A

RESPONSE TO CRITICISMS OF THE BEIR III REPORT

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 percent) 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 percent 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 percent 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 to 50 percent adopted by the BEIR III Committee or of 5 percent adopted by the authors of the UNSCEAR reports are the product of "sheer, unsupported speculation," and adopts a value of 100 percent in his own calculations. Such a value is incompatible with basic Mendelian genetics, however, 100 percent is the value for the regularly inherited diseases, and the values even as high as 50 percent, 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 percent 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 percent although recent unpublished data could raise this figure to about 10 percent. 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 4B

OOCYTE MUTATIONAL SENSITIVITY

OOCYTE MUTATIONAL SENSITIVITY

The mouse dictyate oocyte is the immature stage most similar histologically to the human immature oocyte. A human occyte 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 irradation for women. BEIR III assumed that the female germ cell sensitivity was 44 percent 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 to 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 4C

DOUBLING DOSE CONSIDERATIONS

4C.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 1 Gy and below is two. The bulk of the human data comes from doses estimated to be in this range with 40 percent of the children born to parents who where exposed in the 1 to 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 (0.01 Gy)" (BEIR 1972, 1980). Assuming our central estimate of risk of dominant mutations for conjoint parental exposure is 30×10^{-4} d + 30×10^{-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.

4C.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 case expected per generation.

$$\text{Total number of recessive diseases} = \text{Current incidence} \left(\frac{1}{\text{Doubling dose}}\right)$$

where the current incidence (corrected for 1978 vital statistics) is 1,920 cases and the doubling dose for chronic exposure is 1 Gy, and for acute exposure it is 0.5 Gy.

$$\text{Total number of cases for } 0.01 \text{ Gy} = 1{,}920 \times 0.01 \simeq 20$$

$$\text{Total number of cases for } 0.1 \text{ Gy} = 1{,}920 \times 0.1 \simeq 200$$

$$\text{Total number of cases for } 2 \text{ Gy} = 1{,}920 \times 4 \simeq 7700$$

Appendix 4D

RANGE OF UNCERTAINTIES ASSOCIATED WITH THE INDUCED MUTATION RATE

RANGE OF UNCERTAINTIES ASSOCIATED WITH THE INDUCED MUTATION RATE

In Table 4.D below we provide the estimated induction rate per Gy for each major type of genetic disorder that has been employed to develop our central risk estimates. We also include our lower and upper estimates of these values. They are not derived by statistical considerations, but more accurately reflect our best estimates of the uncertainties associated with our central estimates. These uncertainties stem from both biological and physical considerations.

Dominant: We have used the range of uncertainties developed by BEIR III and in addition assumed that the human female germ cell sensitivity is indeed like the mouse (namely zero) for the lower range in this and all succeeding types of disorders.

X-Linked Disorders: We assume for lower estimates that only males cells are mutable and that only 100 loci on the human X chromosome contribute to disorders. The upper range assumes that 1000 loci (4 x the central estimate) contribute to the total mutation frequency on the X chromosome. For the lower estimate of x-linked disorder there would be zero first generation effects; in subsequent generations the lower range would give 1/5 as many cases as the upper range.

Aneuploidy: Our lower estimate assumes that aneuploidy is not inducible by radiation. Our upper estimate is derived from an ICRP task group calculation.

Unbalanced Translocations: Our lower estimate corresponds to a dose rate reduction factor of 9 which UNSCEAR (1982) employed instead of the factor 2 used in deriving our central estimate, which reduces the male rate by a factor of 4.5. Again we would use zero rate for females. The upper range for the male assumes no dose rate reduction and an RBE of 1 for gamma radiation. Thus for the male the upper estimate is five times larger than the central estimate. For the female, in addition to this factor of 5, we assume that the human immature oocytes, like the mouse mature oocytes, are twice as sensitive as male spermatogonial cells (this has been observed for acute high dose exposures); therefore the upper range for the female will be 10 times larger than the central estimate. To estimate risk of viable unbalanced translocation in first translocations in first generation, correction factors from Section 4.4.3.1 must be applied.

Irregularly Inherited Diseases at Equilibrium: We assume that the doubling dose is 1 Sv for the central estimate, whereas BEIR III assumed a doubling dose range of 0.5 to 2.5 Sv. As stated in Section 4.4.2, the lowest value expected is 1800 cases when the lowest mutation component, 0.05, and the highest doubling dose, 2.5 Gy, are used in the calculation. However, this calculation also assumes that the male and female cells are

equally mutable. If only the male germ cells are mutated then the lowest value expected is 900 cases or 9 x 10^{-4}/Gy induction rate from the male. For the upper estimate, the mutation component is taken to be 0.5 and the relative mutation risk of 2 (1/0.5) is employed based on a doubling dose of 0.5 Gy.

In the table the numbers in parentheses provide the reader with approximate factors by which the number of cases shown in Table 4.1 should be multiplied to obtain either lower or upper estimates.

Table 4.D

Range of Uncertainties Associated with the Induced Mutation Rate

Type of Disorder	Estimate of Induction Rate (10^{-4} Gy^{-1})		
	Central	Lower[a,b]	Upper[a,b]
Dominants[c]			
Male	15	5 } (1/6)	45 } (3)
Female	15	0 }	45 }
X-Linked[d]			
Male	18	7.2 } (0, 1/5)[c]	72 } (4)
Female	18	0 }	72 }
Aneuploid			
Male	5	0 } (0)	15 } (3)
Female	5	0 }	15 }
Unbalanced Translocations			
Male	7.4	1.6 } (1/8)	37 } (7)
Female	5.6	0 }	56 }
Irregularly Inherited Diseases at Equilibrium			
Male	71	9 } (1/16)	450 } (6.4)
Female	71	0 }	450 }
Periimplantation Wastage	480	20 (1/25)	1900 (4)
Aneuploid	360	0 (0)	1080 (3)
Unbalanced Translocations	120	20	820

[a]The numbers in parentheses represent the factor by which the number of cases shown in the Tables 4.1-4.4 should be multiplied to obtain lower or upper estimate values.

[b]To determine range of 30-year period listed in Table 4.1, multiply values by 0.48.

[c]Zero applies to the first generation, one-fifth to later generations.

Appendix 4E

GENETIC DISEASES OF HUMANS (SOME CASES) BY CLASS

GENETIC DISEASES OF HUMANS (SOME CASES) BY CLASS
(UNSCEAR, 1977, Tables 1,2,3,7 [Annex H] with Modifications)

Complexly Inherited Diseases

Anencephalus
Spina bifida with hydrocephalus
Spina bifida without mention of hydrocephalus
Cogenital hydrocephalus
congenital hydrocephalus
Congenital hydrocephalus
Encephalocele
Microcephalus
Anomaliesof Brain
Anomalies of spinal cord
Anomalies of nervous system
Unspecified anomalies of brain, spinal cord, and nervous system
Anophthalmos
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
Brachial cleft, cyst, or fistula; preauricular sinus
Webbing of neck
Anomalies of face and neck
Unspecified anomalies of face and neck
Common trucus
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 arteriosus
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 larynx
Anomalies of larynx, trachea, and bronchus
Cogenital cystic lung
Agenesis of lung
Anomalies of lung
Cleft plalate
Cleft lip
Cleft palate with cleft lip
Anomalies of tongue
Pyloric stenosis
Tracheoesophageal fistula
Esophageal atresia and stenosis
Anomalies of upper alimentary tract
Unspecified anomalies of upper alimentary tract
Meckel diverticulum
Anomalies of intestinal fixation
Hirschsprung 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 digestive system
Unspecified anomalies 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
Agammaglobulinemia
Hypogammaglobulinemia
G-6-PD deficiency anemia
Hereditary hemolytic anemia
Hypochromic anemia with iron loading
Hemophilia A
Hemophilia B
Coagulation defect
Moderate idiopathic mental retardation
Progressive muscular dystrophy
Myotonia atrophica
Color blindness
Unspecified disease of retina and optic nerve
Congenital hydrocephalus
Pseudohermaphroditism
Generalized anomalies of skeleton
Anomalies of skin
Unspecified anomalies of skin, hair, or nails
Syndromes affecting multiple systems

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 disease
Unspecified glycogen storage disease
Galactosemia
Lipid storage disorders
Cystic fibrosis
Hepatolenticular degeneration
Disorders involving metabolism of minerals
Disorders of steroid metabolism
Congenital disorders of metabolism
Agammaglobulinemia
Hypogrammaglobulinemia
Unspecified metabolic diseases
Mediterranean anemia
Aplastic anemia
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 sytem
Microphthalmos
Buphthalmos
Congenital cataract
Anomalies of aorta
Unspecified anomalies of circulatory system
Atresia of biliary ducts
Pseudohermaphroditism
Cystic kidney disease
Chondrodystrophy
Generalized anomalies of skeleton
Anomalies of skin
Syndromes affecting multiple systems

Dominant Disorders

Familial acholuric jaundice
Vascular hemophilia
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 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
Anomalies 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 edema of legs
Anomalies of skin
Unspecified anomalies of skin, hair, and nails
Tuberous sclerosis
Congenital syndrome, affecting multiple systems

Appendix 4F

YEARS OF LIFE LOST FOR GENETIC DISEASES

Years of Life Lost For Genetic Diseases [Table 46-49 in Annex I from UNSCEAR (1982) with modified titles]

Estimates of Load From Monogenic Dominant Disorders

Condition	Frequency per 10^4 births	Average years of Un-Impaired Life	Impaired Life and Degree of Impairment	Lost Life Years	Cause of Death
Familial hypercole-sterolaemia	20	55	10 (50%)	5	Coronary thrombosis
Deafness - congenital (dominant)	1	0	70 (30%)	0	None
Deafness - 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
Hyotonic 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
Martan 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	Frequency per 10^4 births	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	Frequency per 10^4 male births	Average years of Un-Impaired 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
Maemophilia A	1	0	50 (20%)	20	Hemorrhage
X-linked ichthyosis	1	0	70 (15%)	0	None
X-linked forms of mental reduction	1	0	50 (80%)	20	Intercurrent infection

Estimates of Load From Some Selected Chromosomal Disorders

Condition	Frequency per 10^4 births	Average years of Un-Impaired 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 4G

DEMOGRAPHIC DATA AND COMPUTER PROGRAMS

DEMOGRAPHIC DATA AND COMPUTER PROGRAMS

Three programs were written for this report: DOMINANT, X-LINKED, and TRANSLOCATIONS. Each of the programs in 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 demographic data presented in 5-year intervals (the only data readily available) and they project population structure by 5-year intervals (the only data readily available) and they project population structure by 5-year intervals. This means, of course, that the dose projected to result from a nuclear accident must also be accumulated in 5-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 4G.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 an females. Age-specific maternity function for mutant females.

(3) Doses (in rem) by 5-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 normal, balanced, and unbalanced gametes in females and males, respectively; and the segregation ratios in inherited translocation heterozygotes: UNF, 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 5-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 4G.1.

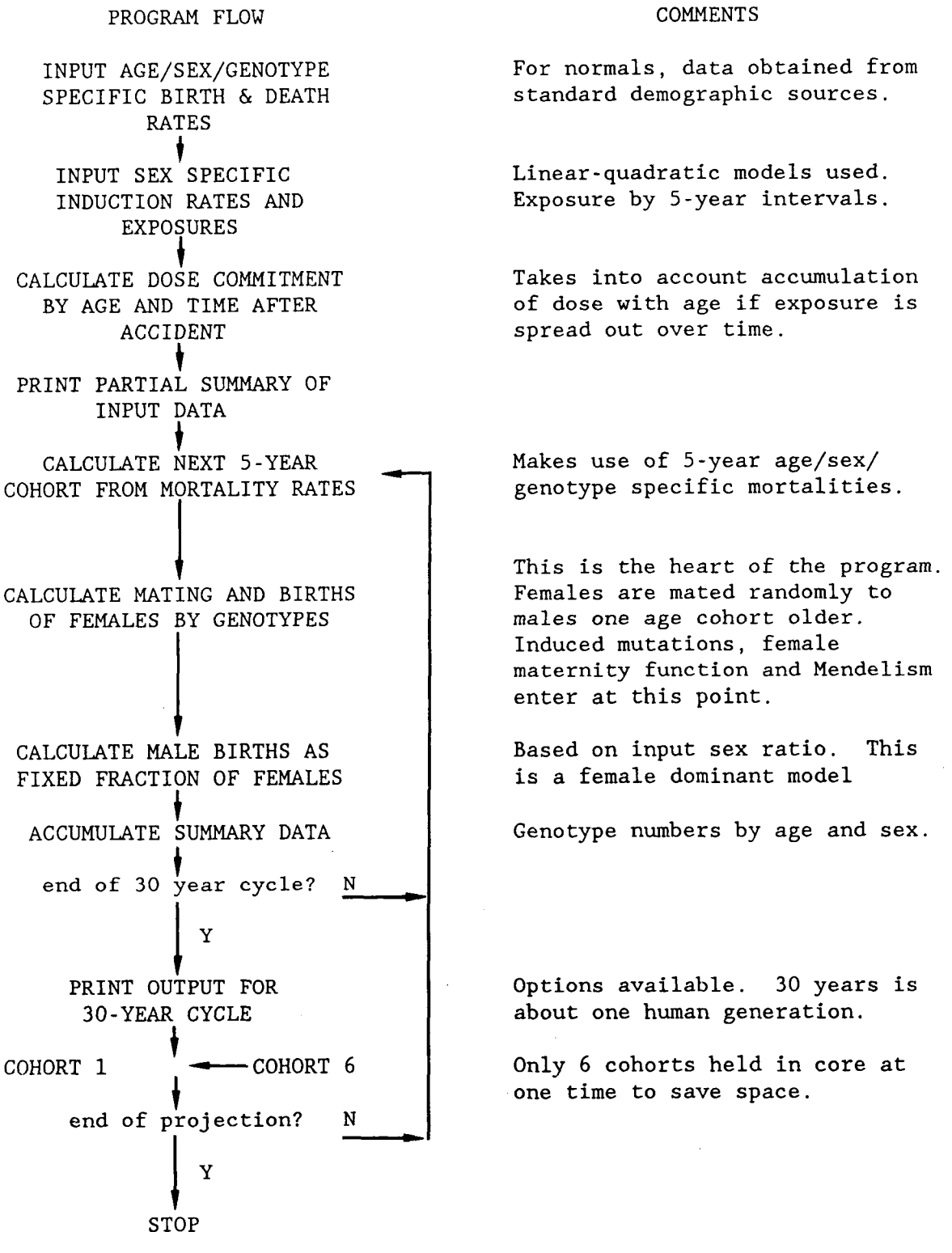

Figure 4G.1. Structure Common to DOMINANT, XLINKED and TRANSLOCATION programs

Table 4G.1 Example Output From the Program XLINKED.

B:USWHT1 S: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	0.000000
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 percent 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 5 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, 5 years after the accident, there have been 44,804 normal male births, 42,355 normal females 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 of 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 5-year interval before the year 2003 produced 39,033 male births, 0.045 hemizygous male births and 0.308 heterozygous female

births. By 2003 there had been a total of 211,435 normal males but the cumulative mutant total is still below 1/2. The total population size is not 1,140,780 (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 any approximately stable population. The population increases at first in USWHT1 because the U.S. population is not in age structure equilibrium.

Summary Key to Printout

BNM = normal male births.
BNF = normal female births.
BMM = mutant (heterozygote) male births.
BMF = mutant (heterozygote) female births.
C...= cumulative...
P...= 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 5 years; used for lethal dominant conditions and aneuploids.

MUTDOMT: Assigns normal survival and fecundity (modified 1978 data) to mutant heterozygotes and zero survival after five 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 survival 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 percent viability to mutant heterozygotes and zero viability to mutant homozygotes. Used for 80 percent viability runs of dominant traits.

MUTXN8: Assigns 80 percent viability to mutant homozygous males and zero viability to mutant homozygous females. Used for 80 percent viability runs of X-linked traits.

APPENDIX 4H

SPONTANEOUS AND RADIATION-INDUCED PERI-IMPLANTATION WASTAGE

SPONTANEOUS AND RADIATION-INDUCED PERI-IMPLANTATION WASTAGE

As we have stated earlier in the main text, there is an enormous amount of spontaneous loss of pregnancy. Estimates reviewed in BEIR III indicate that about one out of every two conceptions naturally abort. Since 90 percent of these cases appear to be lost within the first eight weeks we prefer the term periimplantation wastage since they are usually not even recognized as pregnancies. Studies discussed in UNSCEAR 1977 and 1982 indicate that up to 65 percent of this wastage results from chromosome disorders, the majority of these (some 95 percent) being monosomes, trisomies, and triploids, and 5 percent resulting from unbalanced translocations. The issue of concern for this report is what proportion of additional cases will be induced by radiation exposure.

To compute the number of cases on conceptions that will be lost by aneuploidy we have used the value derived from mouse male studies of Speed and Chandley in UNSCEAR 1982. These authors and other workers have not observed a significant increase over a range of doses when the female mouse is studied. We accept at face value the induced rate observed at 1 Gy and assume it applies equally as well for the female. No dose response or dose-rate experiments have been performed as yet to provide information at low doses. Therefore we apply the same assumption used for aneuploids in the live born population. Namely that our lower estimate is zero and the upper risk estimate will be three times the central estimate. Finally, since this aneuploidy contribution is not transmissible to subsequent generations, the effect (or about 90 percent of it) will only be observed as periimplantation wastage in the first generation.

For the unbalanced translocation component we have used nine times the values calculated for viable unbalanced translocation estimates. This applies for the low central and upper risk estimates as does the same transmissibility factors used between generations.

Table 4.D summarizes the expected ranges for these two contributions. It may well be the case that 90 percent of the cases of loss will occur in the first 8 weeks post conception and would go unrecognized and the remaining cases might occur during the remaining period of gestation.

Appendix A

THYROID EFFECTS

H. Maxon, University of Cincinnati
S. A. Book, University of California
C. R. Buncher, University of Cincinnati
V. Hertzberg, University of Cincinnati
S. R. Thomas, University of Cincinnati

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 NCRP Report 80, "Induction of Thyroid Cancer by Ionizing Radiation" (NCRP, 1985).

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

$$R = \frac{C}{n} \bullet \frac{10^4}{D \bullet y} \qquad (A.1)$$

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 percent (386/4326) of the women and in 1.8 percent (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 percent) 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 percent). 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 percent (Trowbridge et al., 1975).

In calculating the number of expected cancers from the number of total thyroid nodules, 10 percent of the nodules are assumed to be malignant in patients below age 20, and a rate of 12 percent 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 percent 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 percent 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 percent per year) and the incidence in the National Survey (0.0036 percent per year) suggests that registry data underestimate the true incidence by a factor of 2-3. Therefore, the projected incidence of 0.01 percent 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 non-thyroidal 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 percent) 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 percent decrease in risk after 40 years postirradiation. Similarly, in the 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 percent 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 percent of the total population at risk which was Jewish. The relative risk for Jews compared to nonJews was about 3.5 after adjustment for gender, time since irradiation, and radiation dose (Shore, 1980). Gender seemed

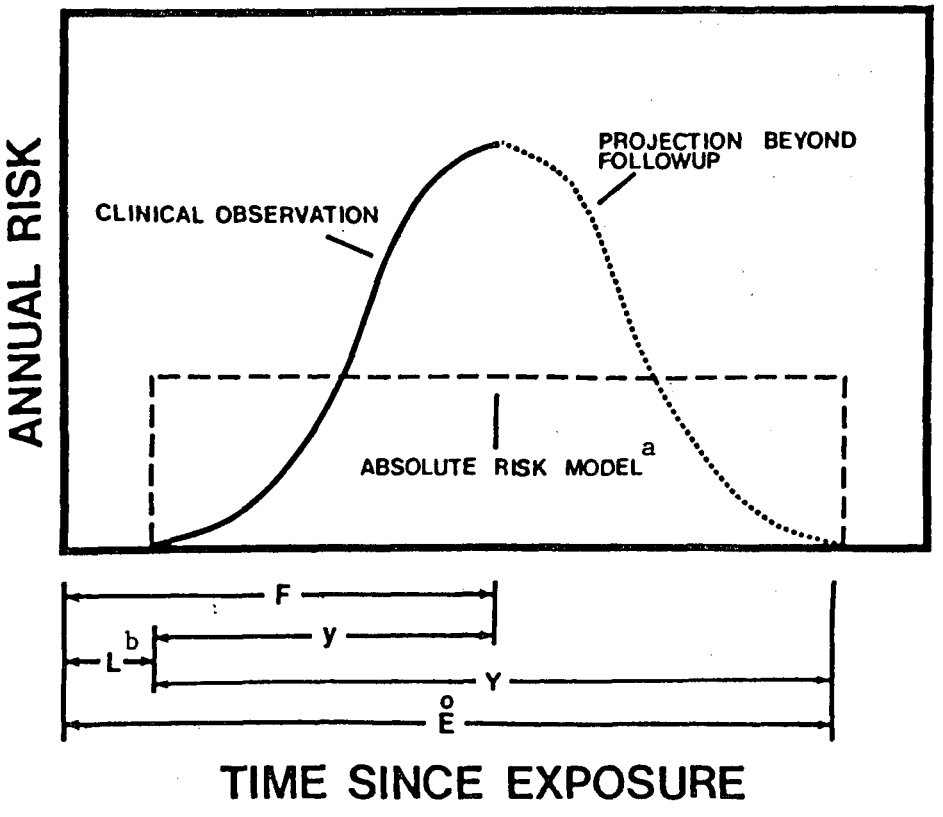

Figure A.1 Annual Risk of Excess Cancer as a Function of Time Since Exposure

Notation Used:

F = Length of clinical followup
L = minimum induction (latency) period
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.

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 percent 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 percent Black and 11 percent 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 percent 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 percent) 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 to 90 percent) of Jewish patients and less than 1 percent 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 percent (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 percent 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 percent 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 percent); among 25 patients examined 40 years or more after exposure, only 1 cancer (4 percent) was found. The average time interval between irradiation and examination for patients with thyroid cancer was 23.8 $\pm$ 7.0 years (range 10 to 40 years), and less than 1

percent 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 x 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.

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 two-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 percent 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 percent 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

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	1,194
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 (%)	Black (%)	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

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 percent 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 T65D 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 T65D 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 percent) 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 percent) 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 percent of these radiation-associated human carcinomas have been of the papillary type and about 10 percent 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 percent of patients with papillary carcinoma of the thyroid had died of the disease and approximately 18 percent 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 percent 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 percent for males and about 9.6 percent for females, for an average of about 10 percent 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 percent 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, ^{136}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 percent in subjects less than 10 years of age at exposure, compared to 6.8 percent in those between 10 and 18 years of age, and 7.1 percent 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 percent, compared to about 3.3 percent in the 10- to 18-year old group; and to about 2.3 percent 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 percent) were found in the 8 percent of the population that is Jewish. This same Jewish population contributed 23 percent 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) (~ 14 cases per 10^4 PY per Gy) and the Michael Reese Hospital study (Frohman et al., 1977) (~ 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 percent nonJewish and 24 percent Black (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 Black 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 percent) had cancer and 77 (89.5 percent) 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 percent, compared to a spontaneous prevalence in Graves' disease of about 0.1 percent. 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 percent

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 percent. 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 percent) and 2086 males (21 percent) 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 percent) occurred in women and 2 (25 percent) 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, 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

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[1]Formerly the Bureau of Radiological Health.

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 to 4 thyroid cancers in children and of about 8 to 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 percent confidence level), one may solve the equation:

$$\text{Largest Number of Excess Cases} = 1 - (0.05)^{1/a}$$

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 percent 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 percent 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 percent 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:

$$n = \frac{\left(Z_\alpha\right)^2 \bullet P_0 \bullet \left(1 - P_0\right)}{\left(P - P_0\right)^2}$$

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 percent (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:

$$\text{Risk} = \frac{n \bullet 10^4}{\text{PY} \bullet \text{Gy at risk}} \left[\frac{(1.645)^2 \left(P_0\right)\left(1 - P_0\right)}{n}\right]^{0.5}$$

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 6.7×10^4 PY • Gy at risk with a spontaneous thyroid cancer rate in the unexposed Swedish population of $8.19 \bullet 10^4$, and for a population of 937 people exposed in childhood and representing $1.4 \bullet 10^4$ PY • Gy with a spontaneous rate of thyroid cancer of about $3 \bullet 10^4$, 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 percent 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 percent 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.

Table A.3

Calculation of Age, Sex, and Radiation Source Specific Risk Estimates for Thyroidal Neoplasms

$$SRE = R \bullet F \bullet S \bullet A \bullet Y \bullet L$$

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.

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 percent of the radiation-induced thyroid cancers will be lethal.

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 percent were positive for antimicrosomal antibodies and that 9 percent 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 percent) and single or multinodular glands were found in 70/319 (21.9 percent). In the 113/416 subjects who underwent thyroid surgery, 14/113 (12.4 percent) had a primary diagnosis of chronic thyroiditis. These findings suggest that chronic thyroiditis occurred at least 12.4 percent 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 percent) 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 percent) patients with a history of external radiation therapy to the thyroid area in childhood had clinical stigmata of chronic lymphocytic

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.

thyroiditis and positive serologic antithyroid autoantibody tests. Studies of rats (Kotani et al., 1982) exposed to 2 to 8 Gy of external radiation have shown a 50 percent incidence of chronic thyroiditis on histologic examination of the thyroid 2 to 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 non-irradiated 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 percent) had chronic thyroiditis, but chronic thyroiditis was the primary diagnosis in only 4/254 (1.6 percent).

A.6.2 Following Exposure to Irradiation from Nuclear Weapons

Asano 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 percent) nonexposed people and in 64/1970 (3.3 percent) irradiated people who had died and undergone autopsy examination during that time. While the overall incidence of chronic thyroiditis increased from 0.2 percent in 1956 to 4.9 percent 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 2 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). Significant systemic symptoms have rarely been associated with massive release of stored thyroid hormone (Shafer and Nuttal, 1971; Krishnamurthy and Blahd, 1974). The syndrome generally resolves within 2 to 4 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 to 5 percent 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 percent within 24 hours and an effective half-life of 6 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 percent) 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 6-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 2,000 Gy) administered for the ablation of residual thyroid tissue after thyroidectomy for thyroid cancer, may induce acute radiation thyroiditis in 90 percent of such patients. The resulting symptoms were found to be severe in two of 57 patients (3.5 percent) 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 percent 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 to 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 ten 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 eight cases per 10^4 PY per Gy. Again, women appeared to be at higher risk than men.

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

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	1,329
Woodard, (1980)	2,872	71	22	1.19	75,189
Maxon, et al., (1980)	1,266	12	11.5	2.90	42,221
Frohman et al., (1977)	1,476	218[c]	18	8.08	214669
Pooled Data	7,829	311	16.2[d]	2.45[d]	333,408

[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.

times greater in subjects under the age of 18 years at exposure and was about 5 times greater for those exposed in uterol (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 3,000 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 to 15 Gy from x-ray and 10 to 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 to 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 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.

Table A.6

Benign Thyroid Changes Following Exposure of Animals 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

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 percent based on a 0.02 percent 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

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 of 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.

experience of patients with Graves' disease exposed to ^{131}I and thus allow estimation of the radiation effects alone on the thyroid gland.

In the Cooperative Thyrotoxicosis Follow-Up Study (Becker et al., 1971), data were collected on 5,221 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 2 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 percent 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 percent per year.

The figure of 0.7 percent 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), 6,000 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 5-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 percent (0.7 percent per year times 5 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 6-day effective half-life, Chapman (1975) found that 22 of 28 (80 percent) 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 percent 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 x 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 hypothyroidism 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 percent per Gy for people exposed at age less than 20 years and 180 percent 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 percent 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 of Exposure 0-19	Age of Exposure ≥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 percent) was about twice what would be predicted for radiation-associated thyroid cancers (10 percent).

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 deaths, over all age groups, occurring in each time interval.

Table A.B.2

Estimated Time Distribution of Total Deaths
Due to Radiation-Associated Thyroid Carcinoma

	Type of Cancer				
Diagnosis (Years)	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 deaths, over all age groups, occurring in each time interval.

[b]Distribution of total deaths due to radiation-associated thyroid cancer, regardless of cell type, over each time period.

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10. SUPPLEMENTARY NOTES

11. ABSTRACT *(200 words or less)*

This report provides dose-response models intended to be used in estimating the radiological health effects of nuclear power plant accidents. Models of early and continuing effects, cancers and thyroid nodules, and genetic effects are provided.

Two-parameter Weibull hazard functions are recommended for estimating the risks of early and continuing health effects. Three potentially lethal early effects—the hematopoietic, pulmonary and gastrointestinal syndromes—are considered. In addition, models are provided for assessing the risks of several non-lethal early and continuing effects—including prodromal vomiting and diarrhea, hypothyroidism and radiation thyroiditis, skin burns, reproductive effects, and spontaneous abortions.

Linear and linear-quadratic models are recommended for estimating cancer risks. Parameters are given for analyzing the risks of seven types of cancer in adults—leukemia, bone, lung, breast, gastrointestinal, thyroid and "other". The category, "other" cancers, is intended to reflect the combined risks of multiple myeloma, lymphoma, and cancers of the bladder, kidney, brain, ovary, uterus and cervix. Models of childhood cancers due to in utero exposure are also provided. For most cancers, both incidence and mortality are addressed. The models of cancer risk are derived largely from information summarized in BEIR III—with some adjustment to reflect more recent studies. The effect of the revised dosimetry in Hiroshima and Nagasaki has not been considered.

Linear and linear-quadratic models are also recommended for assessing genetic risks. Five classes of genetic disease—dominant, x-linked, aneuploidy, unbalanced translocations and multifactorial diseases—are considered. In addition, the impact of radiation-induced genetic damage on the incidence of peri-implantation embryo losses is discussed.

The uncertainty in modeling radiological health risks is addressed by providing central, upper, and lower estimates of all model parameters. Data are provided which should enable analysts to consider the timing and severity of each type of health risk.

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