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Health Effects Models for Nuclear Power Plant Accident Consequence Analysis

Modifications of Models Resulting From Recent
Reports on Health Effects of Ionizing Radiation

Low LET Radiation

Part II: Scientific Bases for Health Effects Models

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Prepared for
U.S. Nuclear Regulatory Commission

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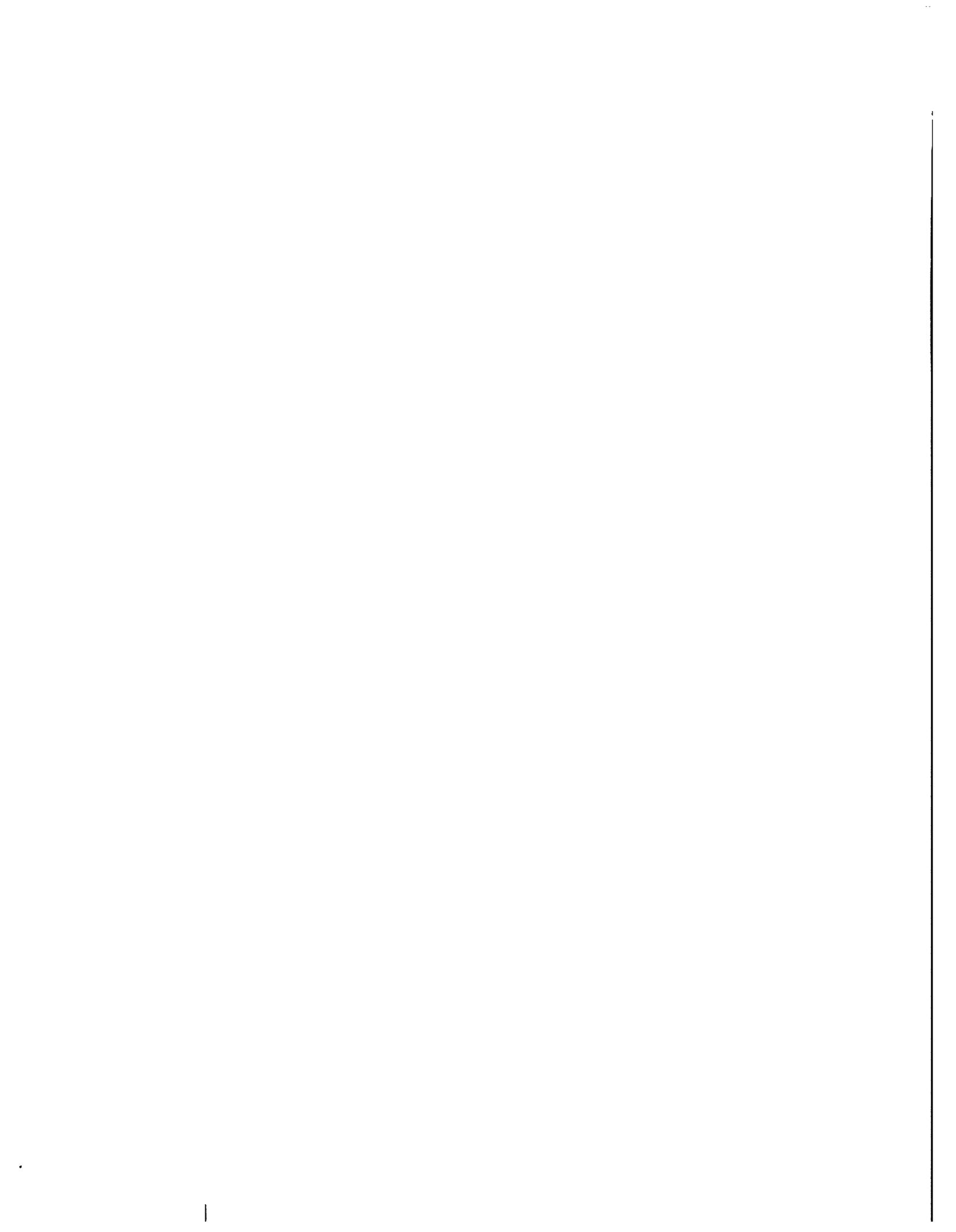
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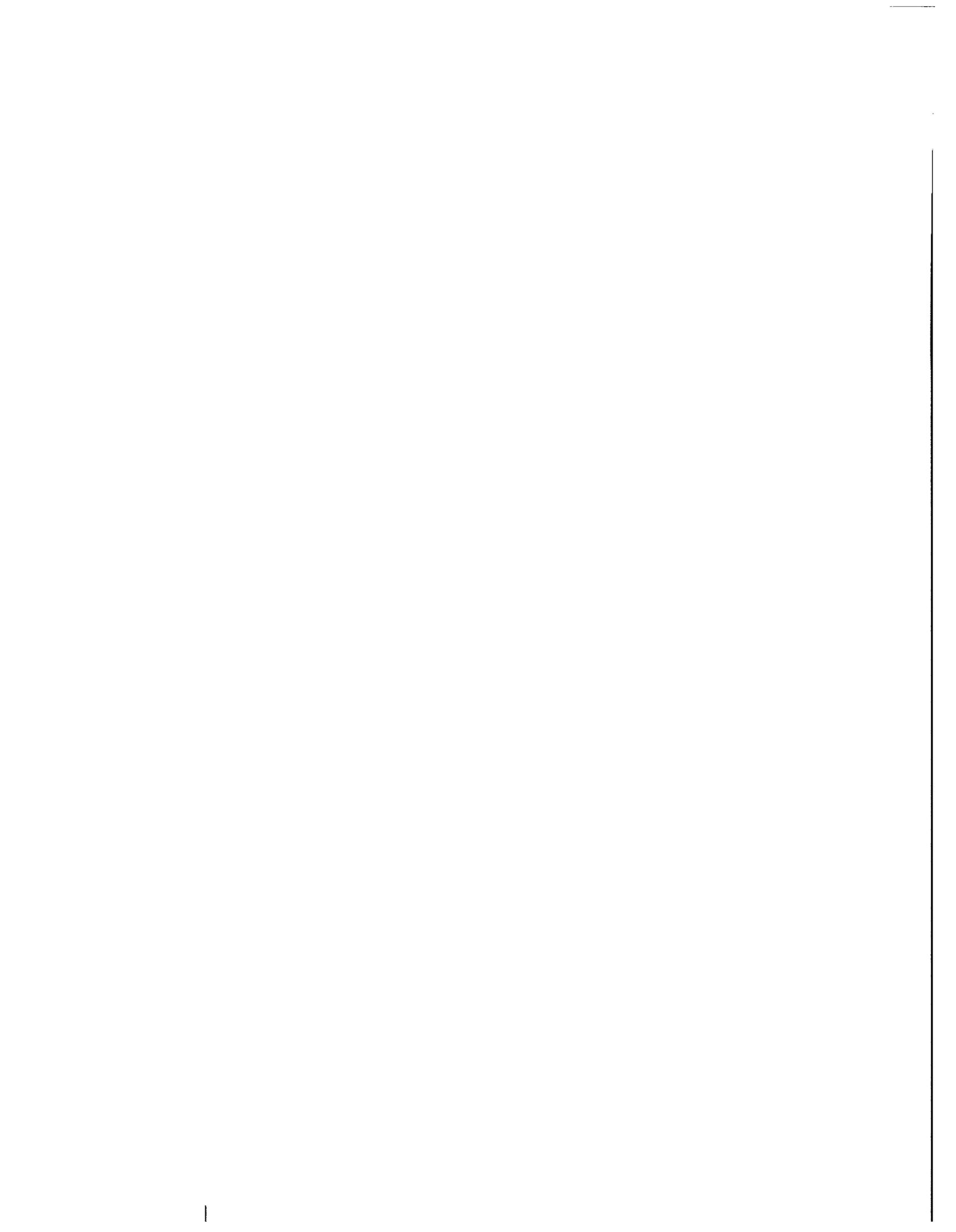
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ABSTRACT

The Nuclear Regulatory Commission has sponsored several studies to identify and quantify the potential health effects of accidental releases of radionuclides from nuclear power plants. The most recent health effects models resulting from these efforts were published in two reports, NUREG/CR-4214, Rev. 1, Part I (1990) and Part II (1989). Several major health effects reports have been published recently that may impact the health effects models presented in these reports. This addendum to the Part II (1989) report, provides a review of the 1986 and 1988 reports by the United Nations Scientific Committee on the Effects of Atomic Radiation, the National Academy of Sciences/National Research Council BEIR V Committee report and Publication 60 of the International Commission on Radiological Protection as they relate to this report. The three main sections of this addendum discuss early occurring and continuing effects, late somatic effects, and genetic effects. The major changes to the NUREG/CR-4214 health effects models recommended in this addendum are for late somatic effects. These changes reflect recent changes in cancer risk factors that have come from longer followup and revised dosimetry in major studies like that on the Japanese A-bomb survivors. The results presented in this addendum should be used with the basic NUREG/CR-4214 reports listed above to obtain the most recent views on the potential health effects of radionuclides released accidentally from nuclear power plants.



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EXECUTIVE SUMMARY

Because of continuing interest in predicting the potential health effects of accidental releases of radionuclides from nuclear power plants, the Nuclear Regulatory Commission has sponsored several studies to identify and quantify these effects through the use of health effects models. The Reactor Safety Study (NRC, 1975) provided the basis for most of the earlier official estimates related to these health effects. Subsequent efforts by NRC-supported groups resulted in improved health effects models that were published in report NUREG/CR-4214 (NRC, 1985) and revised further in report NUREG/CR-4214, Rev. 1, Part II (NRC, 1989)^a.

Several recent reports that may impact on the revised models presented in the NUREG/CR-4214 report are the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1988)^a, the National Academy of Sciences/National Research Council BEIR V Committee (NAS/NRC, 1990)^a, and revised recommendations of the International Commission on Radiological Protection Publication 60 (ICRP 1991)^a. The goal of this addendum is to discuss the health effects models and estimates presented in these recent reports, to compare them with those in the NUREG/CR-4214 report, and to recommend modifications of the health effects models when necessary.

For tracking with the underlying NUREG/CR-4214 report, this addendum is divided into the same three main sections. The first health effects discussed are those categorized as early occurring and continuing effects. This section is followed by a major section on late-occurring somatic effects and a section on genetic effects.

Early Occurring and Continuing Effects

Two publications containing useful information on early and continuing effects of irradiation, UNSCEAR 88 and BEIR V were reviewed to determine if there were aspects of the publications that could affect dose-response models presented in NUREG/CR-4214. For the BEIR V publication, only the mental retardation data, based on Japanese atomic bomb survivors exposed *in utero*, were found suitable for evaluating dose-response models for early and continuing effects presented in NUREG/CR-4214. The model presented in NUREG/CR-4214 for severe mental retardation associated with *in utero* exposure was modified to allow for uncertainty associated with threshold dose.

The UNSCEAR 88 report devoted a large section to early and continuing effects. The LD₅₀ data presented in UNSCEAR 88 was found consistent with the model for hematopoietic death presented in NUREG/CR-4214. There was a large overlap between morbidity data bases used in UNSCEAR 88 and NUREG/CR-4214, and no compelling reasons were found to alter most morbidity models presented in NUREG/CR-4214.

^aThroughout this report, unless noted otherwise, the following report names are used: NUREG/CR-4214 for reference (NRC, 1989); UNSCEAR 86 for reference (UNSCEAR, 1986); UNSCEAR 88 for reference (UNSCEAR, 1988); BEIR III for (NAS/NRC, 1980); BEIR V for (NAS/NRC, 1990); and ICRP 60 for reference (ICRP, 1991).

Late Somatic Effects

Review of the recent reports mentioned above has resulted in many recommended modifications of the NUREG/CR-4214 models, and these recommendations are described in detail below.

As previously, the central estimates are intended to reflect the most realistic assessment of radiation risks, while the upper and lower bounds are intended to reflect alternative assumptions that are also reasonably consistent with available evidence. The bounds particularly reflect uncertainty in the appropriate factor for modifying linear estimates for doses received at low doses and dose rates, but also reflect uncertainty in the choice of risk coefficients and in the method for projecting risks over time. These bounds cannot be regarded as confidence limits, since it is not feasible to associate a level of probability with them.

The most important recommended changes in the NUREG/CR-4214 models are as follows: First, the recommended dose and dose rate reduction factors (DDREF) for calculating central and lower bound estimates for low dose and low dose rate exposure have been modified. The previous factor of 3.3 for the central estimates has been changed to 2, and the previous factor of 10 for the lower bound has been changed to 4. Second, it is recommended that central estimates for most cancer types be based on age-specific coefficients rather than the non-age-specific treatment employed earlier. Finally, many of the risk coefficients have been modified to account for recent data and analyses, particularly analyses of the Japanese A-bomb survivors based on revised dosimetry.

Although it is unlikely that all body organs would be irradiated uniformly in a reactor accident, for the purpose of summarizing and comparing risk estimates, it is useful to consider the total cancer risk if all organs received the same dose. In this case, the sum of the revised site-specific central lifetime risk estimate for exposure received at low doses and dose rates is about 500 fatal cancers per 10^4 person-Gy, compared with an estimate of 200 given in NUREG/CR-4214. The revised lower and upper bounds are about 100 and 1100 fatal cancers per 10^4 person-Gy, respectively, compared to the previous bounds of 40 and 900 per 10^4 person-Gy. The central estimate is the same as the estimate of 500 fatal cancers per 10^4 person-Gy provided by ICRP 60 as adapted from UNSCEAR 88, but lower than the BEIR V linear estimate of 800 fatal cancers per 10^4 person-Gy. However, BEIR V recommends that a reduction factor of 2 or more be applied for doses received at low rates, leading to comparability with the recommended central estimate.

The following text details recommended modifications of the NUREG/CR-4214 models to account for the results of recent analyses and recommendations given in the BEIR V, UNSCEAR 88, and ICRP 60 reports.

a. Modification of Reduction Factors for Low Doses and Dose Rates

To obtain central and lower bound estimates in NUREG/CR-4214, linear estimates for most cancer types were reduced for low doses and dose rates. It is recommended that the factors used for this reduction be modified as follows. For leukemia, bone cancer, lung cancer, skin cancer, and other cancers, linear estimates should be reduced by a DDREF to obtain central and lower bound estimates when the total dose is less than 0.2 Gy, and for higher doses when the dose rate is less than 0.1 Gy per hour. The DDREF to be applied for the central

estimates is 2, and that for the lower bound estimates is 4. The DDREF of 4 should also be applied in obtaining lower bound estimates for breast cancer. The linear-quadratic functions indicated in NUREG/CR-4214 should not be applied.

b. Use of Age at Exposure-Specific Coefficients

The central estimates for breast cancer, lung cancer, gastrointestinal cancers, and other cancers should be based on the age-specific rather than on the non-age-specific estimates. Age-specific estimates were used in NUREG/CR-4214 for upper bound estimates for these cancer types.

c. Modifications in Risk Coefficients

Several changes in risk coefficients are recommended, and apply to both cancer mortality and cancer incidence. The reasons for these changes are discussed in Section 3.4, and the new coefficients are summarized in Tables 3.20 and 3.21.

The absolute risk coefficient for obtaining upper bound, central, and lower bound estimates for leukemia should be increased by a factor of 2, and that for bone cancer by a factor of 4. The modified linear risk coefficients are then 4.5 per 10^4 PYGy (person-year-Gy) for leukemia and 0.4 per 10^4 PYGy for bone cancer.

The excess relative risk coefficients used to obtain the upper bound estimate for breast cancer in women should be 1.0 per Gy for those exposed under age 20, and 0.4 per Gy for those exposed at age 20 and over, very similar to those used previously. The excess relative risk coefficients used to obtain central estimates should be 0.7 per Gy for those exposed under age 20, 0.3 per Gy for those exposed between 20 and 40, and 0.1 per Gy for those exposed at age 40 and over. Previously, the coefficient 0.45 per Gy was used for all exposure ages.

The excess relative risk coefficients used to obtain the upper bound estimate for lung cancer should be increased from 1.11 to 1.5 per Gy for those exposed under age 20, and from 0.37 to 0.5 per Gy for those exposed at age 20 and over. The age-specific risk coefficients used to obtain the central estimate for lung cancer should be 0.6 per Gy for those exposed under age 20 and 0.3 per Gy for those exposed at age 20 and over, compared to the non-age-specific coefficient of 0.18 per Gy used previously. The absolute risk coefficient used to obtain the lower bound estimate for lung cancer mortality should be increased from 2.0 to 2.5 per 10^4 PYGy. The absolute risk coefficient used to obtain the lower bound estimate for lung cancer incidence should be increased from 2.2 to 2.7 per 10^4 PYGy.

The absolute risk coefficient used to obtain the lower bound estimate for fatal gastrointestinal cancer should be increased from 2.7 to 4.0 per 10^4 PYGy. The corresponding coefficient for calculating gastrointestinal cancer incidence should be increased from 4.6 to 6.8 per 10^4 PYGy.

The excess relative risk coefficients used to obtain the upper bound and central estimates for other cancer should be increased from 0.6 to 1.1 per Gy for those exposed under age 20, and from 0.2 to 0.25 per Gy for those exposed over age 20. The absolute risk coefficients used to obtain lower bounds should be increased from 1.5 to 3.5 per 10^4 PYGy for mortality and from 2.9 to 6.8 per 10^4 PYGy for incidence.

For skin cancer, the upper bound and central estimates should be based on a relative risk projection model, using a coefficient of 0.5 per Gy. The absolute risk coefficient for the lower bound estimate should be increased from 2.0 to 6.7 per 10^4 PYGy.

d. Comparison of Modified Estimates with BEIR V, UNSCEAR 88 and ICRP 60

Tables 3.8 and 3.9 present comparisons for linear estimates from NUREG/CR-4214 with estimates from BEIR V, UNSCEAR 88, and ICRP 60. Tables 3.16 and 3.17 show these same comparisons using NUREG/CR-4214 estimates as modified by the above recommendations. Table 3.18 shows a comparison of excess deaths in those exposed under 20 years of age for the modified NUREG/CR-4214 model and BEIR V. The BEIR V estimates in Table 3.18 were obtained from Table 3.5 as the average of estimates for males and females exposed at ages 5 and 15.

The reasons for differences in estimates obtained from various models are discussed in the text, especially in Section 3.4.

e. Tables Summarizing the New Model

Tables 3.19-3.22 are revised versions of Tables 3.1-3.3, and 3.5, respectively, from NUREG/CR-4214. These tables incorporate the recommended modifications.

Genetic Effects

With one exception, the irregularly inherited diseases, the UNSCEAR 86 and BEIR V genetic effect estimates are similar to those adopted by NUREG/CR-4214, and no changes are recommended. For irregularly inherited diseases, UNSCEAR 86 and BEIR V do not contain numerical estimates, but ICRP 60 does. It is recommended that the NUREG/CR-4214 recommendation for this class of genetic effects be changed to include the new natural incidence estimates of irregularly inherited diseases and their corresponding estimates of induced cases for both the first generation and accumulated over all generations, recognizing, however, the great uncertainties associated with these estimates. It is also recommended that the class of congenital abnormalities be treated separately.

ACKNOWLEDGEMENTS

As was true for the underlying report for which this report is an addendum, NUREG/CR-4214, Rev. 1, Part II (1989), a number of authors have contributed sections. Because of the direct connection between this addendum and the 1989 NUREG report, it was fortunate that the authors of this addendum were authors or co-authors of the respective chapters in the 1989 report. These authors were Dr. Bobby Scott, Inhalation Toxicology Research Institute; Dr. Ethel Gilbert, Battelle Pacific Northwest Laboratory; Dr. Seymour Abrahamson, University of Wisconsin; and Dr. Michael Bender, Brookhaven National Laboratory. Dr. Bruce Boecker, Inhalation Toxicology Research Institute, coordinated the preparation of this report.

Beginning with the preparation of the original NUREG/CR-4214 report in 1985 and continuing during the preparation of the 1989 revised NUREG/CR-4214 report, an Advisory Committee has provided valuable input. To carry forward the quality and consistency of these reports to this addendum, a number of members of the Advisory Committee served as authors or reviewers of this addendum:

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Every effort has been expended to respond to the comments of all these reviewers. Recognizing that such an extensive review process can, at times, generate diverging opinions on certain points, the authors have used their best scientific judgement in preparing the final version of this report.

1.0 INTRODUCTION

Several reports addressing the health risks resulting from exposure to ionizing radiation have recently become available. These include the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 1988)^a, the National Academy of Sciences/National Research Council BEIR V Committee (NAS/NRC, 1990)^a, and revised recommendations of the International Commission on Radiological Protection given in Publication 60 (ICRP, 1991)^a. These reports consider recent epidemiologic and experimental data and analyses of these data that were not available when the original NUREG/CR-4214 (NRC, 1985) was published. Of particular importance are new analyses of the Japanese A-bomb survivor data, which are based on revised DS86 dosimetry, and on a follow-up period through 1985. Although some of this new material was considered in the 1989 revision of NUREG/CR-4214^a (NRC, 1989), the revision did not attempt a full evaluation of this new material, and analyses based on DS86 dosimetry were not available in 1987 when these revisions were made.

The goal of this addendum is to discuss the risk models and estimates presented in the reports noted above, to compare them with those used in the NUREG/CR-4214 report, and to recommend modifications of the NUREG/CR-4214 models when needed. This addendum is not intended to provide a complete revision of the previous models that takes account of all available data, but rather to suggest modifications when new data provide strong evidence that old assumptions and risk coefficients are no longer appropriate. Where available evidence is consistent with different models and a wide range of risk coefficients, preference has been given to choices that lead to lifetime risk estimates that are reasonably comparable to those provided in other recent reports. In general, the approach is to keep modifications to a minimum and as simple as possible. That some features of models provided by UNSCEAR 88 or BEIR V are not incorporated should not necessarily be interpreted as a judgment that these features are inappropriate.

This addendum is not intended to be used as a "stand alone" document, but must be used with the revised 1989 version of NUREG/CR-4214. The addendum is divided into three main parts corresponding to the three main sections in the NUREG/CR-4214 report. The first health effects discussed are those categorized as early occurring and continuing effects. This section is followed by a major section on late occurring somatic effects and a section on genetic effects.

^aThroughout this report, unless noted otherwise, the following report names are used: NUREG/CR-4214 for reference (NRC, 1989); UNSCEAR 86 for reference (UNSCEAR, 1986); UNSCEAR 88 for reference (UNSCEAR, 1988); BEIR III for (NAS/NRC, 1980); BEIR V for (NAS/NRC, 1990); and ICRP 60 for reference (ICRP, 1991).

2.0 EARLY OCCURRING AND CONTINUING EFFECTS

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2.1 Introduction

Since the research that led to the publication of NUREG/CR-4214 was initiated, three additional publications containing useful information on early and continuing effects of irradiation have become available, UNSCEAR 88, BEIR V and ICRP 60. In this section, we discuss those aspects of the latter publications that could affect models for early occurring and continuing effects of irradiation presented in NUREG/CR-4214. In particular, we are interested in whether or not information provided in the publications indicates a need to change the dose-response models for early occurring and continuing effects of low-LET irradiation.

2.2 BEIR V

The main focus of the BEIR V publication was on late somatic and genetic effects of irradiation. However, a small section of this publication was devoted to early occurring and continuing effects of irradiation and included useful information on the following: (1) mental retardation occurring as a result of irradiation *in utero*; (2) cataracts of the lens of the eye; and (3) fertility and sterility. Only the data for mental retardation were suitable for use in evaluating the dose-response models presented in NUREG/CR-4214.

On the basis of studies of Japanese A-bomb survivors irradiated *in utero*, it was concluded, as reported in BEIR V, that the prevalence of radiation-induced mental retardation was highest in persons irradiated during the 8-15 week period after conception, was less in those irradiated between 16-25 weeks after conception, and was negligible or absent in those irradiated either before 8 weeks or later than 25 weeks after conception. For those irradiated during the 8-15 week, post-conception period, the prevalence of mental retardation appeared to increase with dose in a manner consistent with a linear, nonthreshold response. A linear exponential model was also consistent with the data. The risk at 1 Gy was estimated to be about 43% under the DS86 dosimetry with the linear model and 48% with the linear-exponential model. However, the data do not exclude a threshold in the 0.1 - 0.2 Gy region (Otake *et al.*, 1989). Evidence for a threshold is stronger for the 16-25-week, post-conception period than for the 8-15-week period. The lower estimate of the threshold is 0.21 Gy for the 16-25 week period.

The BEIR V publication also included a discussion of some of the uncertainties associated with these estimates, including the number of cases; the appropriateness of the comparison groups; errors in the estimates of the absorbed dose and calculated prenatal ages at exposure; variation in the severity of mental retardation, and other confounding factors, including malnutrition and diseases.

2.3 ICRP 60

The ICRP Publication 60 provides only limited information related to early occurring and continuing effects of irradiation. The information provided relates to deterministic effects resulting from irradiation *in utero*. Estimates of threshold dose and the risk at 1 Gy are the same as provided in BEIR V, based on children exposed *in utero* at Hiroshima and Nagasaki. For the 8-15 weeks, post-conception period, a threshold with a lower estimate of 0.12 to 0.2 Gy is given.

2.4 UNSCEAR 88

Unlike BEIR V, UNSCEAR 88 devoted a rather large section to early and continuing effects, including a discussion of the Chernobyl and Goiânia accident data. The early and continuing effects of irradiation discussed included prodromal symptoms, acute lethality, and damage to specific organs or tissues (skin, oral mucosa, eye, lung, testis, and ovary). However, dose-response models for specific effects were not provided. There was a large overlap between the morbidity data bases used in UNSCEAR 88 and NUREG/CR-4214, so that there is no compelling reason to alter the morbidity models presented in NUREG/CR-4214 on the basis of information given in UNSCEAR 88.

More data on acute lethality in humans from radiation-induced injury were reviewed in UNSCEAR 88 than in NUREG/CR-4214. The major findings are summarized below:

- 1) The most recent estimates of the $LD_{50/60}$ from the Japanese data, based on DS86 dosimetry, have yielded values of around 3.0 Gy. This estimate is thought to be applicable to individuals receiving no medical treatment or only minimal treatment after irradiation. However, the UNSCEAR publication also pointed out that the $LD_{50/60}$ could be as low as 2.5 Gy for these treatment categories.
- 2) Shielding of as little as 10% of the active marrow in humans may reduce the acute mortality to zero after doses near the $LD_{50/60}$.
- 3) The ratio LD_{90}/LD_{10} is about 2.
- 4) For healthy humans receiving good supportive medical treatment after irradiation, the LD_{50} could approach about 5 Gy.

These conclusions are consistent with the acute lethality model presented in NUREG/CR-4214, in that the model places the LD_{50} for individuals receiving only minimal medical treatment after irradiation, in the range 2.5-3.5 Gy, and for those with good supportive medical treatment, in the range 3.7-5.3 Gy, for uniform, total-body exposure to gamma radiation at high dose rates.

2.5 Recommended Changes in Models

Based on these considerations, it is recommended that the NUREG/CR-4214 model for mental retardation be modified to allow for uncertainty about threshold dose.

The following changes in the model are recommended for the 8-15 week period:

- 1) For central estimates of prevalence, a 0.1-Gy threshold, based on BEIR V and ICRP 60, should be used with the NUREG/CR-4214 model.
- 2) For upper bounds on the prevalence, no threshold should be used.
- 3) For lower bounds on the prevalence, a 0.2-Gy threshold, based on BEIR V and ICRP 60, should be used.

The D_{50} doses of 1.5, 1.0, and 3.1 Gy presented in NUREG/CR-4214 for generating central, upper, and lower estimates of prevalence, respectively, for the 8-15 week period, should be retained and used with the thresholds indicated in 1-3 above.

The following changes are recommended for the 16-25 week period:

- 1) For central estimates of prevalence, a 0.2-Gy threshold, based on BEIR V, should be used with the NUREG/CR-4214 model.
- 2) For upper bounds on the prevalence, no threshold should be used.
- 3) For lower bounds on the prevalence, a 0.5-Gy threshold, a rounded midrange of estimates provided by Otake, *et al.*, 1989, should be used.

The D_{50} doses of 7.1, 3.1, and 10.0 Gy presented in NUREG/CR-4214 for generating central, upper, and lower estimates of prevalence of mental retardation, respectively, for the 16-25 week period, should be retained and used with the threshold indicated above.

2.6 Summary

Three publications containing useful information on early and continuing effects of irradiation, UNSCEAR 88, BEIR V and ICRP 60, were reviewed to determine if there were aspects of the publications that could affect dose-response models presented in NUREG/CR-4214. From the BEIR V and ICRP 60 publications, only the mental retardation data, based on Japanese atomic bomb survivors exposed *in utero*, were found suitable for evaluating dose-response models for early and continuing effects presented in NUREG/CR-4214. The dose-response model for severe mental retardation presented in NUREG/CR-4214 was modified to allow for uncertainty about threshold dose.

The UNSCEAR 88 report devoted a large section to early and continuing effects. The LD_{50} data presented in UNSCEAR 88 were found to be consistent with the model for hematopoietic death presented in NUREG/CR-4214. There was a large overlap between morbidity data bases used in UNSCEAR 88 and NUREG/CR-4214, and no compelling reasons were found to alter morbidity models presented in NUREG/CR-4214.

3.0 LATE SOMATIC EFFECTS

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3.1 Introduction

Three reports addressing risks of late somatic effects resulting from exposure to radiation have recently been published. These are the UNSCEAR 88, BEIR V and ICRP 60 reports. These reports include data and analyses that were not available when the NUREG/CR-4214 revision was prepared. The availability of new dosimetric information and additional followup time for the Japanese A-bomb survivors is a particularly important resource for the evaluation of late-occurring somatic effects.

This section is divided into three main parts. In the first part, Section 3.2, summaries of the models and recommendations from UNSCEAR 88, BEIR V and ICRP 60 are given. In Section 3.3, several issues involved in risk assessment are considered with discussion and comparison of how each was handled in the three recent reports and in NUREG/CR-4214. Section 3.4 reviews the models for each type of cancer, and makes specific recommendations regarding modifications of these models. Section 3.5 summarizes the recommended modifications.

3.2 Overview of Recent Risk Assessment Reports, and Comparison with Estimates from NUREG/CR-4214

3.2.1 UNSCEAR 88

UNSCEAR 88 provides lifetime risk estimates for fatal cancer based on both multiplicative and additive risk projection models for leukemia, all cancer except leukemia, and for the following separate cancer categories: bladder, breast, colon, lung, multiple myeloma, ovary, esophagus, stomach, and remainder. Estimates of the loss of life expectancy are also provided. For all cancers, separate estimates are given for the total population, for a working population (aged 25-64 years), and for an adult population (25 and older). These estimates are reproduced in Tables 3.1-3.3.

The summary lifetime risks provided by UNSCEAR 88 were based on a model in which the risk coefficients were assumed not to depend on sex, and, for Tables 3.1 and 3.2, the coefficients were assumed not to depend on age at exposure. Estimates in Table 3.3 were calculated in two ways, allowing the coefficients to depend on age at exposure by using age-specific risk coefficients for exposure ages (0-9, 10-19, and 20+) and using a single age-averaged coefficient for all ages. Minimal latent periods were the same as those used in NUREG/CR-4214 (2 years for leukemia; 10 years for other cancers). Risk coefficients were based on the A-bomb survivors with an RBE of 1 as presented in Shimizu *et al.* (1990). A linear dose-response function was

Table 3.1 (from UNSCEAR 88)

Projection of excess lifetime mortality for specific cancers. Expressed as number of deaths per 10⁴ persons exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate (Based on the population of Japan. 90% confidence intervals in parentheses.)

Malignancy	Multiplicative risk projection model	Additive risk projection model
Leukemia	97 (71 - 130)	93 (77 - 110)
All cancers other than leukemia	610 (480 - 750)	360 (280 - 440)
Bladder	39 (16 - 73)	23 (11 - 40)
Breast ^a	30 (14 - 53)	22 (11 - 35)
Colon	79 (36 - 134)	29 (14 - 46)
Lung	151 (84 - 230)	59 (34 - 88)
Multiple myeloma	22 (6 - 51)	9 (3 - 17)
Ovary ^a	15 (4 - 34)	13 (4 - 24)
Esophagus	34 (8 - 72)	16 (3 - 31)
Stomach	126 (66 - 199)	86 (45 - 131)
Other organs	114 ^b	103 ^b
	118 ^c	66 ^c
Total	707 ^d	453 ^d
	712 ^e	416 ^e

^a These estimates apply to the entire population and are one-half the risks for females.

^b This value is derived by subtracting the sum of the risks at the sites listed (bladder, breast, colon, lung, multiple myeloma, ovary, esophagus, and stomach) from the risks for all cancers other than leukemia.

^c This value is derived by fitting a linear relative risk model to the basic cancer data after the exclusion of those cases of cancer at the specific sites listed.

^d Leukemia plus all other cancers.

^e Leukemia plus other individual sites including other organs.

Table 3.2 (from UNSCEAR 88)

Projection of loss of life expectancy for specific cancers. Expressed as years of life lost per person per Gy of organ absorbed dose of low-LET radiation at high dose rate (Based on the population of Japan. 90% confidence intervals in parentheses.)

Malignancy	Multiplicative risk projection model	Additive risk projection model
Leukemia	0.22 (0.16 - 0.27)	0.30 (0.25 - 0.36)
All cancers other than leukemia	0.73 (0.57 - 0.90)	0.91 (0.71 - 1.10)
Bladder	0.03 (0.01 - 0.06)	0.04 (0.02 - 0.07)
Breast ^a	0.06 (0.03 - 0.09)	0.06 (0.03 - 0.09)
Colon	0.09 (0.04 - 0.15)	0.07 (0.04 - 0.12)
Lung	0.17 (0.09 - 0.25)	0.15 (0.09 - 0.22)
Multiple myeloma	0.03 (0.0 - 0.06)	0.02 (0.01 - 0.04)
Ovary ^a	0.03 (0.01 - 0.06)	0.04 (0.01 - 0.06)
Esophagus	0.04 (0.01 - 0.08)	0.04 (0.01 - 0.08)
Stomach	0.15 (0.07 - 0.23)	0.22 (0.11 - 0.33)
Other cancers	0.14 ^b	0.28 ^b
	0.14 ^c	0.17 ^c
Total	0.95 ^d	1.2 ^d
	0.94 ^e	1.1 ^e

^a These estimates apply to the entire population and are one-half the risks for females.

^b This value is derived by subtracting the sum of the risks at the sites listed (bladder, breast, colon, lung, multiple myeloma, ovary, esophagus, and stomach) from the risks for all cancers other than leukemia.

^c This value is derived by fitting a linear relative risk model to the basic cancer data after the exclusion of those cases of cancer at the specific sites listed.

^d Leukemia plus all other cancers.

^e Leukemia plus other individual sites including other cancers.

Table 3.3 (from UNSCEAR 88)

Summary of projections of lifetime risks for 10⁴ persons (5000 males and 5000 females) exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate (Based on the population of Japan)

	Risk projection model	Excess fatal cancers	Years of life lost
Total population ^a	Additive	400 ^a - 500 ^b	9,500 ^a - 12,000 ^b
	Multiplicative	700 ^b - 1,100 ^a	9,500 ^b - 14,000 ^a
Working population (aged 25-64 years)	Additive	400 ^b - 600 ^a	8,800 ^b - 13,300 ^a
	Multiplicative	700 ^a - 800 ^b	8,200 ^a - 9,700 ^b
Adult population ^b (over 25 years)	Additive	500 ^b	8,400 ^b
	Multiplicative	600 ^b	6,200 ^b

^a Based on age-specific risk coefficients.

^b Based on constant (age-averaged) risk coefficients.

used for extrapolation, but the UNSCEAR 88 Committee recommended reducing the effects at low doses (< 0.2 Gy) and low dose rates (<0.05 mGy per minute) by a factor between 2 and 10, but no specific recommendation regarding the exact factor was made. The general method for calculating lifetime risks is similar to that described in NUREG/CR-4214. However, the 1982 population of Japan was used to provide both survival information and baseline risks for application of the multiplicative risk projection model.

Lifetime risk estimates based on certain alternative assumptions were also considered. Projections were made based on risk coefficients obtained from the ankylosing spondylitis patients (mostly males) and from cervical cancer patients (females). Baseline rates for the United Kingdom were used in both cases, with male rates used for the ankylosing spondylitis patients, and female rates used for the cervical cancer patients. In addition, the effect of using both survival information and baseline risks from the United Kingdom, and from Puerto Rico was considered in deriving lifetime risk estimates using coefficients from the Japanese A-bomb survivors.

For thyroid effects, the UNSCEAR 88 report endorses the model provided by the NCRP (1985), a model that is very similar to that used in NUREG/CR-4214. No estimates of skin or bone cancer risks are given, and no attempt was made to estimate cancer incidence (including non-fatal cancers).

3.2.2 BEIR V

The BEIR V report updates the models and risk estimates provided in the earlier report of the BEIR III Committee, published in 1980 (NAS/NRC, 1980). The BEIR III report played a strong role in determining the models and risk estimates included in NUREG/CR-4214. Unlike the UNSCEAR 88 models, BEIR V models were developed for application to the United States population. Thus, consideration of the recent report of the BEIR V Committee is especially important.

BEIR V provides estimates for excess mortality from leukemia and cancers other than leukemia expected to result from a single exposure to 0.1 Sv, from continuous lifetime exposure to 1 mSv per year, and from continuous exposure to 0.01 Sv per year from age 18 until age 65. Estimates of the number of excess deaths (with confidence limits), the total years of life lost, and the average years of life lost per excess death are given. Separate estimates are provided for males and females. These estimates are reproduced in Table 3.4. The overall BEIR V estimate is that a single exposure of 0.1 Sv to a population of 100,000 of all ages would result in 800 extra cancer deaths.

BEIR V gives additional detail for the single exposure scenario. In this case, mortality estimates for leukemia (ICD codes 204-207), breast cancer (ICD code 174), respiratory cancer (ICD codes 160-163), digestive cancer (ICD codes 150-159), and other cancers (ICD codes 140-149, 170-173, 180-203, 208-209) are given for both sexes and nine age at exposure groups. These estimates are reproduced in Table 3.5. BEIR V also provides models for breast and thyroid cancer incidence, but no lifetime risk estimates are presented.

BEIR V provides estimates that are consistently higher than those in BEIR III, and this is attributed to several factors including the use of a linear dose response model for cancers other than leukemia, revised dosimetry for the Japanese A-bomb survivors, and additional follow-up of the A-bomb survivors and other cohorts. BEIR III employed constant relative and absolute risk models, with separate coefficients for each of several sex and age at exposure groups, while BEIR V developed models in which the excess relative risk is expressed as a function of age at exposure, time after exposure, and sex for each of several cancer categories. BEIR III models were based on the assumption that absolute risks are comparable between the A-bomb survivors and the U.S. population, while BEIR V models were based on the assumption that relative risks are comparable. For a disease such as lung cancer, where baseline risks in the U.S. are much larger than those in Japan, the BEIR V approach leads to much larger risk estimates than the BEIR III approach.

For BEIR V, the reference population and the source of age-specific cancer rates was the 1980 U.S. population. The method used in BEIR V for calculating the number of fatal cancers differs from that employed in UNSCEAR 88, NUREG/CR-4214, and BEIR III in that radiation-induced cancers that occur in persons who would eventually develop cancer without radiation exposure are not counted. This has the effect of reducing risks by a factor of about 0.8.

The models and risk coefficients in BEIR V were derived through analyses of relevant epidemiologic data including the Japanese A-bomb survivors, ankylosing spondylitis patients, Canadian and Massachusetts fluoroscopy patients (breast cancer), New York postpartum mastitis patients (breast cancer), Israel Tinea capitis

Table 3.4 (from BEIR V, 1990)

Excess cancer mortality estimates and their statistical uncertainty - lifetime risks per 100,000 exposed persons^a

	Male			Female		
	Total	Cancers other than leukemia ^b	Leukemia ^c	Total	Cancers other than leukemia	Leukemia
Single exposure to 0.1 Sv (10 rem)	770	660	110	810	730	80
90% confidence limits ^d	540-1,240	420-1,040	50-280	630-1,160	550-1,020	30-190
Normal expectation	20,510	19,750	760	16,150	15,540	610
% of normal	3.7	3.3	15	5	4.7	14
Total years of life lost	12,000			14,500		
Average years of life lost per excess death	16			18		
Continuous lifetime exposure ^e to 1 mSv/y (0.1 rem/y)	520	450	70	600	540	60
90% confidence limits ^d	410-980	320-830	20-260	500-930	430-800	20-200
Normal expectation	20,560	19,760	790	17,520	16,850	660
% of normal	2.5	2.3	8.9	3.4	3.2	8.6
Total years of life lost	8,100			10,500		
Average years of life lost per excess death	16			18		
Continuous exposure ^e to 0.01 Sv/y (1 rem/y) from age 18 until age 65	2,880	2,480	400	3,070	2,760	310
90% confidence limits ^d	2,150-5,460	1,670-4,560	130-1,160	2,510-4,580	2,120-4,190	110-910
Normal expectation	20,910	20,140	780	17,710	17,050	650
% of normal	14	12	52	17	16	48
Total years of life lost	42,200			51,600		
Average years of life lost per excess death	15			17		

^a Based on an equal dose to all organs and the committee's preferred risk models - estimates rounded to nearest 10.

^b Sum of respiratory, breast, digestive, and other cancers.

^c Estimates for leukemia contain an implicit dose rate reduction factor.

^d Additional sources of uncertainty are discussed in BEIR V (1990), Annex 4F.

^e A dose rate reduction factor has not been applied to the risk estimates for solid cancers.

Table 3.5 (from BEIR V, 1990)

Cancer excess mortality by age at exposure and site for 100,000 persons of each age exposed to 0.1 Sv (10 rem)

MALES						
Age at exposure	Total	Leukemia	Cancers other than leukemia			
			Total	Respiratory	Digestive	Other
5	1,276	111	1,165	17	361	787
15	1,144	109	1,035	54	369	612
25	921	36	885	124	389	372
35	566	62	504	243	28	233
45	600	108	492	353	22	117
55	616	166	450	393	15	42
65	481	191	290	272	11	7
75	258	165	93	90	5	-
85	110	96	14	17	-	-
Average ^a	770	110	660	190	170	300

FEMALES							
Age at exposure	Total	Leukemia	Cancers other than leukemia				
			Total	Breast	Respiratory	Digestive	Other
5	1,532	75	1,457	129	48	655	625
15	1,566	72	1,494	295	70	653	476
25	1,178	29	1,149	52	125	679	293
35	557	46	511	43	208	73	187
45	541	73	468	20	277	71	100
55	505	117	388	6	273	64	45
65	386	146	240	-	172	52	16
75	227	127	100	-	72	26	3
85	90	73	17	-	15	4	-
Average ^a	810	80	730	70	150	290	220

^a Averages are weighted for the age distribution in a stationary population having U.S. mortality rates and have been rounded to the nearest 10.

patients (thyroid cancer), and Rochester thymus patients (thyroid cancer). Models for leukemia, respiratory cancer, digestive cancer, and other cancer used only the A-bomb survivor data, although results of analyses of the ankylosing spondylitis patients were considered. A-bomb survivor analyses were based on revised DS86 dosimetry with an assumed RBE of 20 for neutrons, and were restricted to doses less than 4 Gy. Estimates of risks of fatal cancers other than leukemia were obtained by summing the estimates for breast cancer, respiratory cancer, digestive cancer, and other cancer.

For leukemia, a linear-quadratic model was found to provide a significantly better fit to the data than a linear one, and leukemia risks were based on a linear-quadratic function. For low doses, this reduces effects by a factor of 2 over estimates that would have been obtained from the linear model. For other cancers, linear models were found to provide an adequate fit to the data, and were used for extrapolation to low doses. However, the BEIR V Committee recommended reducing these linear estimates by a factor between 2 and 10 for doses received at low dose rates. No specific recommendations regarding the exact factor or the magnitude of the dose rate were made, and no reduction was included in estimates presented in Tables 3.4 and 3.5.

For each cancer category examined, the excess relative risk was modeled as a function of sex, age at exposure, and time after exposure. Specifically, the age-specific risk at dose D is given as

$$\lambda(D) = \lambda_0 [1 + f(D) g(\beta)]$$

where f is a linear or linear-quadratic function of dose of the form $\alpha_1 D$ or $\alpha_2 D + \alpha_3 D^2$, and $g(\beta)$ expresses the dependence of risks on factors such as sex, age at exposure, and time after exposure. The models chosen for calculating lifetime risk estimates were selected based on results of analyses of relevant epidemiologic data. These models are summarized in Table 3.6 and Figures 3.1 - 3.4, and discussed in Section 3.3 and 3.4.

BEIR V provides an assessment of the uncertainty in its lifetime risk estimates, which was accomplished using Monte Carlo simulations to evaluate uncertainty in the lifetime risks resulting from the sampling error in the estimated parameters for the various models. The 90% confidence limits based on these simulations are given in Table 3.4. An advantage of using models developed directly from data (as in BEIR V) is that a more rigorous assessment of uncertainty is possible. However, some sources of uncertainty could not be evaluated using this approach and are not reflected in the intervals presented in Table 3.4. These sources include the appropriateness of risk estimates derived from the Japanese A-bomb survivors for the U.S. population, the extent to which risks are reduced for exposures at low doses and dose rates, and uncertainties in the dosimetry for Japanese A-bomb survivors and other exposed populations from which risk estimates were derived. BEIR V supplements its Monte Carlo simulations by evaluating lifetime risks using selected alternative models, and subjectively assessing uncertainty from selected sources that could not be evaluated statistically.

Table 3.6

**Excess relative risk^a per Gy based on BEIR V leukemia model
(Based on linear term of linear-quadratic model)**

Time since exposure (years)	Age at exposure (years)	
	≤ 20	> 20
2-15	32	}
15-25	2.6	
25-30	0	1.3
30+	0	0

^a The excess relative risk is the ratio of the excess risk resulting from radiation exposure and the baseline risk.

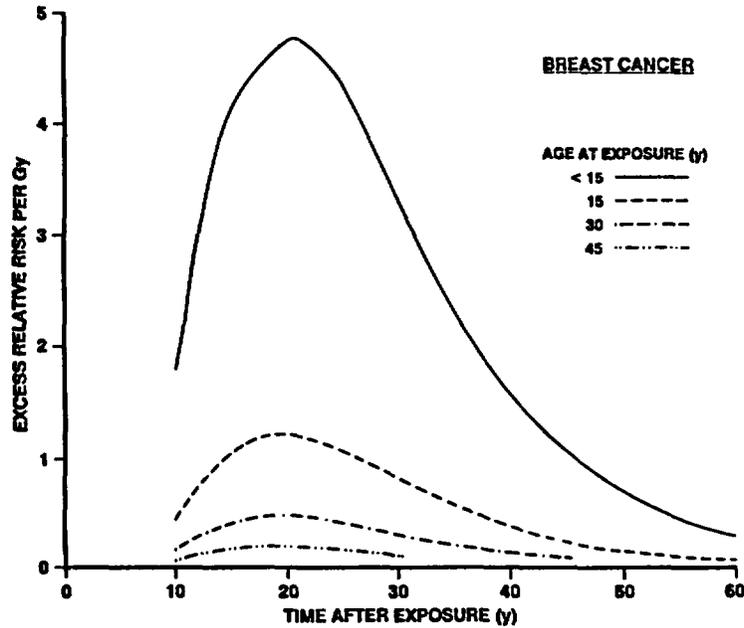


Figure 3.1 - BEIR V model for breast cancer (The excess relative risk is the ratio of the excess risk resulting from radiation exposure and the baseline risk.)

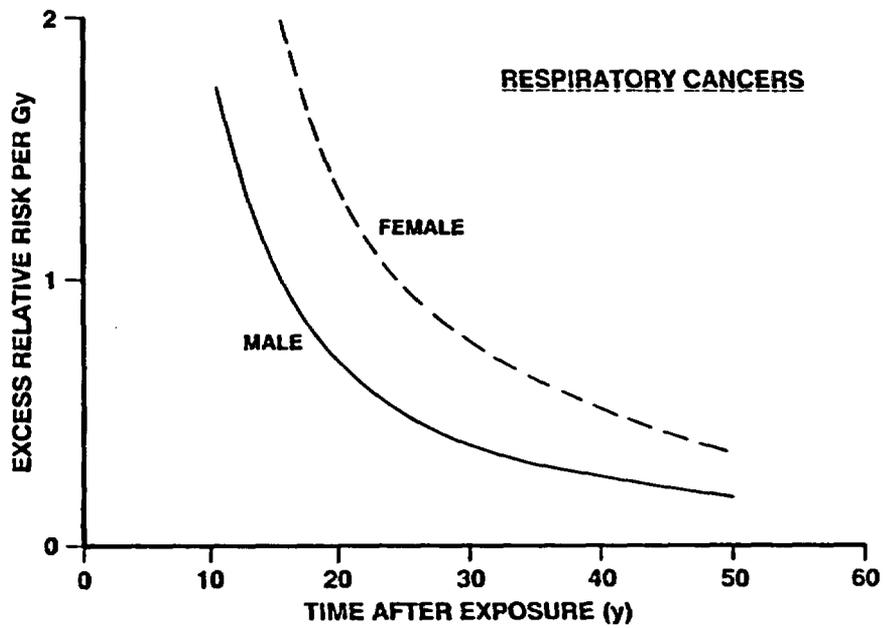


Figure 3.2 - BEIR V model for respiratory cancers (The excess relative risk is the ratio of the excess risk resulting from radiation exposure and the baseline risk.)

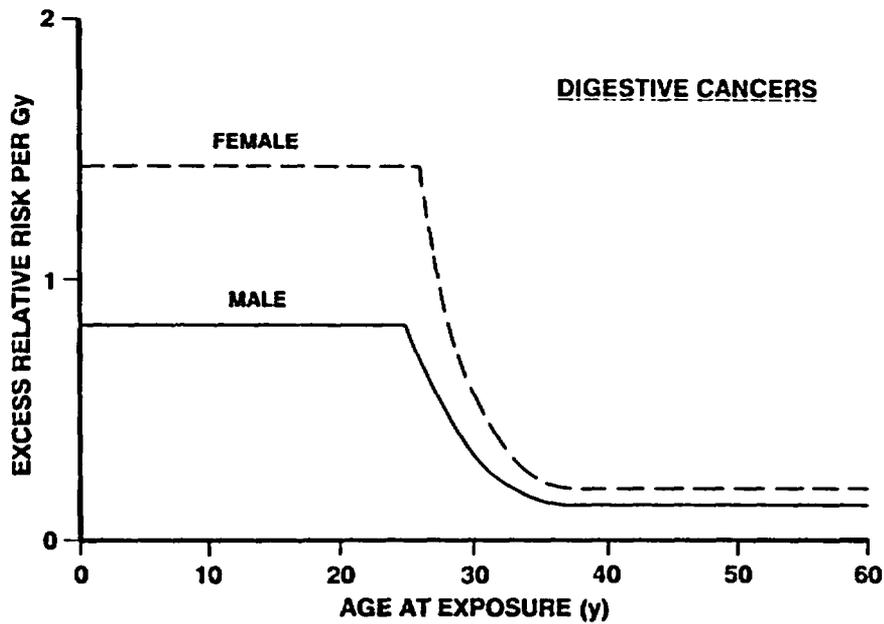


Figure 3.3 - BEIR V model for digestive cancers (The excess relative risk is the ratio of the excess risk resulting from radiation exposure and the baseline risk.)

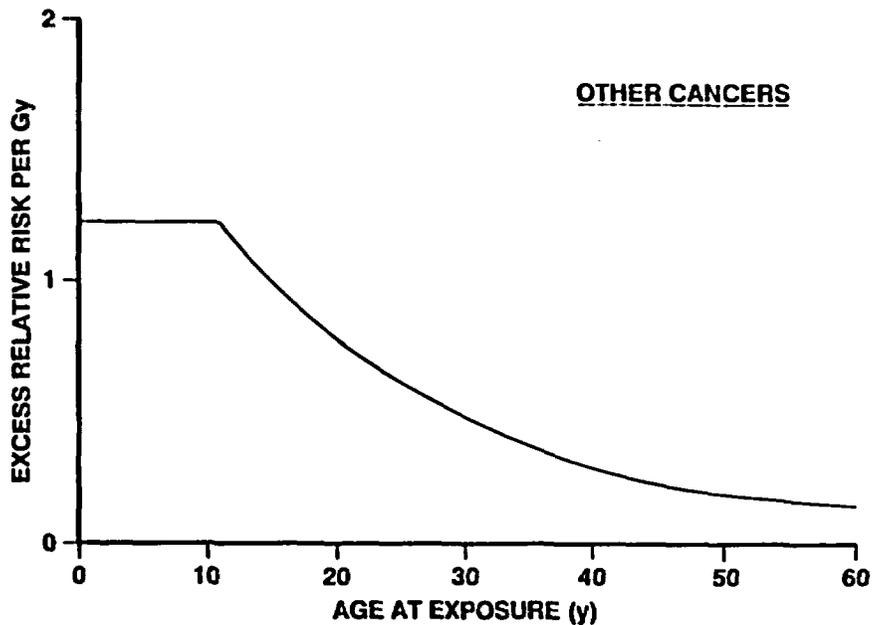


Figure 3.4 - BEIR V model for other cancers (The excess relative risk is the ratio of the excess risk resulting from radiation exposure and the baseline risk.)

3.2.3 ICRP 60

The International Commission on Radiological Protection in its Publication 60 (ICRP, 1991) reviewed estimates provided by the UNSCEAR 88 and BEIR V Committees. The ICRP 60 adopted the age-specific leukemia estimate based on the UNSCEAR additive model, but recommended the age-specific multiplicative model for cancers other than leukemia. The ICRP 60 also recommended that for exposures below 0.2 Gy or below 0.1 Gy per hour, the linear risk estimates obtained from high dose data be reduced by a factor of two. Based on these recommendations, the ICRP 60 risk estimate for a reference population of working age is 400 fatal cancers per 10^4 per Sv, while the estimate for the total population, including children, is 500 fatal cancers per 10^4 per Sv. These numbers are obtained by reducing the relevant UNSCEAR estimates provided in Table 3.3 by a factor of 2.

The ICRP 60 was especially concerned with developing weighting factors to indicate the relative sensitivity to different types of cancers. To obtain these weighting factors, lifetime risks were calculated using age-specific risk coefficients from the Japanese A-Bomb survivors. These lifetime risks were calculated using reference populations from five countries (Japan, United States, United Kingdom, Puerto Rico and China) based on three projection models. The projection models were the additive model, the multiplicative model based on

the assumption that excess risks are proportional to baseline risks across populations, and a multiplicative model based on the assumption that excess (absolute) risks are constant across populations (i.e., independent of baseline risks). The third model was called the NIH model (NIH, 1985) by the ICRP 60.

For cancers of the thyroid, bone surface, skin, and liver, the ICRP 60 considered sources of data other than the Japanese A-bomb survivors to determine estimates. A summary of the risks of fatal cancer from the ICRP 60 report is reproduced in Table 3.7.

Finally, although the ICRP 60 did not present risk estimates for cancer incidence, in developing measures of detriment, the number of non-fatal cancers were considered. These were estimated using site-specific lethality fractions based on both 5-year and 20-year survival rates obtained from the National Cancer Institute.

Table 3.7
ICRP 60 estimates of lifetime risk of fatal cancer
(per 10⁴ person-Gy)

Bone marrow	50
Bone surface	5
Lung	85
Thyroid	8
Breast	20
Colon	85
Esophagus	30
Stomach	110
Liver	15
Ovary	10
Bladder	30
Skin	2
Other cancers	50
Total	500

3.2.4 Comparison of Linear Lifetime Risk Estimates from NUREG/CR-4214 with those from BEIR V, UNSCEAR 88, and ICRP 60

The lifetime risk estimates in NUREG/CR-4214 were obtained by first calculating linear risk estimates, and then modifying these linear estimates by reduction factors to account for low doses and dose-rates. In Tables 3.8 and 3.9, the linear estimates for excess lifetime mortality and loss of life expectancy from NUREG/CR-4214, BEIR V, UNSCEAR 88, and ICRP 60 are presented for comparison. There are many reasons for differences in these estimates, but it seems useful to examine how NUREG/CR-4214 estimates compare with those given in these recent reports. Because it seems appropriate to consider the issue of reducing effects because of low doses and dose-rates separately, the NUREG/CR-4214 estimates in Tables 3.8 and 3.9 have not been modified by reduction factors. Discussion of the reduction factors and recommendations for modification in these factors is given in Section 3.3.1.

For NUREG/CR-4214, both the upper bound estimates and the linear estimates used to obtain the central and lower bound estimates are given. For most cancer types, the upper bound estimates were calculated using different risk coefficients for those under age 20 at exposure than for those over age 20, while central estimates were obtained from linear estimates based on a single coefficient for all ages at exposure. For lung cancer, the upper limit was based on the assumption that relative risks, rather than absolute risks, are comparable between the A-bomb survivor and U.S. populations. All other estimates were based on the assumption that absolute risks are comparable across the two populations. With the exception of leukemia, central and upper bound estimates for the cancer types presented in Tables 3.8 and 3.9 were based on the multiplicative model for extrapolating risks over time. Lower bound estimates were based on the additive model for extrapolating risks over time.

The BEIR V estimates presented in Tables 3.8 and 3.9 were obtained from Table 3.5 by averaging estimates for males and females. However, the leukemia estimate given in Table 3.5 was based on a linear-quadratic model and was doubled to obtain the linear estimate given in Table 3.8. UNSCEAR 88 estimates were given for both multiplicative and additive extrapolation models using a single risk coefficient for all ages at exposure. UNSCEAR also provided estimates for leukemia and for all cancer except leukemia with separate age at exposure coefficients for ages 0-9, 10-19, 20+, and these are also shown in Table 3.9. Age-specific estimates for specific sites would have been larger than the non-age-specific UNSCEAR estimates presented. In comparing estimates, it should be noted that the NUREG/CR-4214 and BEIR V estimates are intended for a U.S. population, while the UNSCEAR and ICRP 60 estimates are intended for international use (although UNSCEAR estimates were based on a Japanese population.)

With the exception of leukemia, the BEIR V and UNSCEAR 88 multiplicative models yield very similar lifetime risk estimates in spite of the fact that the models used in the two reports differ in many respects. In general, the BEIR V, UNSCEAR 88, and ICRP 60 results are more comparable to the upper bounds from NUREG/CR-4214 than to the central estimates, but the comparison varies by cancer type. The ICRP 60 total was obtained from the UNSCEAR 88 multiplicative age-specific model, but the distribution among cancer types was based on consideration of cancer death rates in five countries, and differs from both the UNSCEAR 88 and BEIR V distributions. The NUREG/CR-4214 estimates for leukemia and other cancers are especially low

Table 3.8

Linear lifetime risk estimates^a for fatal cancer. Excess deaths per 10⁴ person-Gy for a population of all ages and both sexes^b

Type of cancer	NUREG/CR-4214			BEIR V ^c	UNSCEAR 88		ICRP 60
	Lower bound	Central	Upper bound		Multiplicative	Additive	
Leukemia	48	48	48	190 ^d	97 (100 ^e)	93 (100 ^e)	100
All cancers other than leukemia	237	382	659	695	610 (970 ^e)	360 (970 ^e)	900
Breast ^f	43	60	87	35	30	22	40
Lung	53	67	245	170	151	59	170
Gastrointestinal	91	189	327	230	239	131	480
Other	50	96	169	260	190	148	210
Total	285	430	707	885	707 (1070 ^e)	452 (420 ^e)	1000

^a This table is presented for the purpose of comparing linear risk estimates, without consideration of modification by dose and dose rate reduction factors. For this reason, estimates have not been modified to account for low doses and dose rates. Thus, the NUREG/CR-4214 central estimates for most cancers in this table are a factor of 3.3 higher, the NUREG/CR-4214 lower bounds are a factor of 10 higher, the BEIR V estimate for leukemia is a factor of 2 higher, and the ICRP 60 estimates are a factor of 2 higher than modified estimates would be.

^b The NUREG/CR-4214 and BEIR V estimates are based on the U.S. population, the UNSCEAR 88 estimates are based on the population of Japan, and the ICRP 60 estimates are based on the populations of the U.S., United Kingdom, Japan, Puerto Rico, and China.

^c Unlike estimates from other reports, BEIR V estimates do not include radiation-induced cancer deaths in persons who would have died of cancer later, and would be about 25% higher had these deaths been included.

^d This is the linear estimate, and is double the linear-quadratic estimate provided by BEIR V for low doses and dose-rates.

^e These estimates were based on age-specific risk coefficients. The UNSCEAR estimates not in parentheses were based on constant (age-averaged) risk coefficients.

^f These estimates apply to the entire population, and are one-half the risks for females.

Table 3.9

Linear lifetime risk estimates^a for fatal cancer
years of life lost per person per Gy^b

Type of cancer	NUREG/CR-4214			BEIR V ^c	UNSCEAR 88	
	Lower bound	Central	Upper bound		Multiplicative	Additive
Leukemia	0.17	0.17	0.17		0.22	0.30
All cancers other than leukemia	0.54	0.55	1.14		0.73	0.91
Breast ^d	0.10	0.10	0.15		0.06	0.06
Lung	0.10	0.10	0.36		0.17	0.15
Gastrointestinal	0.22	0.22	0.40		0.28	0.33
Other	0.12	0.13	0.23		0.23	0.38
Total	0.71	0.72	1.31	1.33	0.95 (1.40 ^e)	1.21 (1.20 ^e)

^a This table is presented for the purpose of comparing linear risk estimates, without consideration of modification by dose and dose rate reduction factors. For this reason, estimates have not been modified to account for low doses and dose rates. Thus, the NUREG/CR-4214 central estimates for most cancers in this table are a factor of 3.3 higher, and the NUREG/CR-4214 lower bounds are a factor of 10 higher than the modified estimates would be.

^b The NUREG/CR-4214 and BEIR V estimates are based on the U.S. population of all ages, and the UNSCEAR 88 estimates are based on the population of Japan.

^c Unlike estimates from other reports, BEIR V estimates do not include radiation-induced cancer deaths in persons who would have died of cancer later.

^d These estimates apply to the entire population, and are one-half the risks for females.

^e These estimates were based on age-specific risk coefficients. The UNSCEAR estimates not in parentheses are based on constant (age-averaged) risk coefficients.

relative to those provided in more recent reports, while the NUREG/CR-4214 estimates for breast cancer are high relative to the newer estimates. The reasons for the discrepancies shown in Tables 3.8 and 3.9 are addressed in subsequent sections.

BEIR V presents estimates for loss of life expectancy for all cancers combined, but not for specific types of cancer. For this reason, comparisons of the two models and recommendations for modifications of NUREG/CR-4214 models are based mainly on the numbers of excess deaths. It is recognized that the ratio of excess deaths provided by different models is not necessarily the same as the ratio of the numbers of years of life lost. This occurs because the number of years lost per death depends on the distribution of deaths by age as well as on the total number of deaths.

3.3 General Problems in Determining Lifetime Risk Estimates

Several general problems that arise in developing risk estimates for different types of cancer are discussed in this section. With the exception of the effects of low doses and dose rates (Section 3.3.1), recommendations for handling these problems are deferred to Section 3.4.1, where the models for several specific categories of cancer are discussed.

3.3.1 Effects of Low Doses and Dose Rates

In NUREG/CR-4214, the central and lower bound estimates for most cancer types were obtained by modifying the linear risk estimates by the factor $a + cD$ (where D is the dose in Gy), resulting in a linear-quadratic function of dose. (Other differences in the upper bound, central, and lower bound estimates are described in Table 3.1 of NUREG/CR-4214.) For doses received at low dose rates (<0.05 Gy per day), effects were modified by the factor a . For central estimates, the values $a = 0.3$, $c = 0.47$ were used, with a obtained as the midpoint of the range of 0.1 to 0.5 suggested by NCRP (1980). For the lower bound estimates, the values $a = 0.1$, $c = 0.6$ were used. Note that the values of 0.3 and 0.1, chosen for a , correspond to DDREFs of 3.3 and 10, respectively.

Estimates provided in BEIR V (except leukemia) were based on linear extrapolation with the recommendation that effects be reduced for doses received at low-dose rates. In some places in BEIR V, a dose rate effectiveness factor (DREF) of 2 or more is recommended, while in other places, a specific DREF of 2 is indicated. BEIR V does not recommend reducing risk estimates for cancers other than leukemia for low doses received at high dose rates. UNSCEAR 88 recommends reducing risks for doses less than 0.2 Gy or for dose rates less than 0.05 mGy per minute (0.072 Gy per day) by a factor between 2 and 10. ICRP 60 recommends a specific DREF of 2 for total doses less than 0.2 Gy, and for larger doses received at rates less than 0.1 Gy per hour (2.4 Gy per day).

The ICRP 60 recommendation was based on evaluation of evidence presented by the NCRP (1980), in addition to more recent experimental evidence. In particular, ICRP 60 notes that the DREF range of 2 to 10 given by NCRP was based on a much greater range of doses and dose-rates than are encountered in human experience,

that epidemiologic data are generally well fit by linear functions, and that some human data show little evidence of fractionation effects while other data indicate effects up to 3 or 4 at most. Clearly, there is much uncertainty in the appropriate factor to be used for reducing effects resulting from exposure at low doses and dose rates. The value of 0.2 Gy, as the cutpoint for applying the DDREF, was apparently chosen because effects have not been observed in the Japanese A-bomb survivor studies below this dose level.

Based on these recent reports, especially the discussion provided in ICRP 60, it is recommended that the previous reduction factors used to obtain central and lower bound estimates be modified. The DDREF to be applied for the central estimates should be changed from 3.3 to 2, while the DDREF to be applied for the lower bound estimates should be changed from 10 to 4. The uncertainty regarding the choice of DDREF is thus reflected by a factor of 2 about the central estimate choice.

The linear-quadratic functions indicated in NUREG/CR-4214 should not be applied as none of the reports (UNSCEAR 88, BEIR V, ICRP 60) recommend reduction of effects for doses over 0.2 Gy that are received at high dose rates. Instead, the following procedure should be used. For leukemia, bone cancer, lung cancer, skin cancer and other cancers, linear estimates should be reduced by DDREFs of 2 and 4, respectively, to obtain central and lower bound estimates when the total dose is less than 0.2 Gy, and for larger doses when received at dose rates less than 0.1 Gy per hour. The DDREF of 4 should also be applied in obtaining lower bound estimates for breast cancer. For application in a specific exposure scenario, the dose received at rates greater than or equal to 0.1 Gy per hour should be calculated. If this dose exceeds 0.2 Gy, the DDREF should not be applied to this portion of the dose. If this dose is less than 0.2 Gy, the DDREF should be applied, and should also be applied to all dose received at rates less than 0.1 Gy per hour.

Most exposure is expected to be received at low doses and dose rates, so that not using the linear-quadratic function as previously done is unlikely to greatly modify predicted effects for most exposure scenarios. The changes in the recommended DDREF (from 3.3 to 2 for central estimates, and from 10 to 4 for lower bound estimates) obviously results in an important increase in risk estimates.

3.3.2 Time after Exposure and 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, and thus lifetime risks can be estimated only by making assumptions regarding the magnitude of risks for the period of life for which no data are available. The problem is especially severe for those exposed early in life. For example, those A-bomb survivors who were under 10 at the time of exposure would be between 40 and 50 in 1985, the date to which current analyses extend. The majority of cancers generally occur at ages older than this.

Appropriate assumptions for extrapolating risks over time are generally determined by examining the pattern of risks over the period for which data are available. The primary models considered in past efforts to estimate lifetime risks are the multiplicative model, in which risks are assumed to be proportional to baseline risks, and the additive model, in which risks are assumed to be constant over time and independent of baseline risks. In NUREG/CR-4214, central and upper bound estimates for cancers of the breast, lung, gastrointestinal system,

and other cancers were based on a multiplicative model. Lower bound estimates for these cancer categories were based on the additive model, as were all estimates for leukemia, bone cancer, skin cancer, and thyroid disease. For leukemia and bone cancer, the period of positive risk was assumed to be from 2 to 27 years following exposure, while for other cancers, this period extended from 10 years following exposure to the end of life (except for thyroid disease for which a 5-year minimal latent period was assumed).

UNSCEAR 88 presents estimates based on both multiplicative and additive models with the period of risk for leukemia extending from 2 to 40 years following exposure, and the period for other cancers extending from 10 years following exposure to the end of life. ICRP 60 expresses a preference for the age-specific additive UNSCEAR model for leukemia, and the age-specific multiplicative UNSCEAR model for other cancers.

The BEIR V Committee conducted analyses of data from the A-bomb survivors and other cohorts that specifically examined the dependence of the excess relative risk on time after exposure. A lack of dependence would correspond to the multiplicative or constant relative risk model. As a result of these analyses, the BEIR V model for leukemia was based on a risk period of 2-25 years from exposure (with a decrease in risks after 15 years) for those exposed under age 20, and a risk period of 2-30 years for those exposed over age 20 (with a drop in risks after 25 years). For other cancers, risks were assumed to persist from 10 years following exposure to the end of life. However, the BEIR V models incorporate a decrease in relative risks with time after exposure for respiratory cancer and breast cancer. These decreases reduce lifetime risks for these cancers over those that would be obtained using a constant relative risk model.

3.3.3 Projection of Risks Across Populations

The application of risk estimates based on the A-bomb survivor population to estimating risks for the current U.S. population requires making assumptions about the comparability of risks in the two populations. For calculating central and upper bound estimates for gastrointestinal and other cancers, and for central estimates for lung cancer given in NUREG/CR-4214, it was assumed that additive excess risks were comparable in the two populations. In calculating risks based on this assumption, additive or absolute risks for the Japanese A-bomb survivors were 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 then served as the estimated excess relative risk coefficient to be applied to U.S. rates in calculating lifetime risks. This approach is referred to in this report as the "additive transportation model". This model was used in BEIR III and in the Radioepidemiological Tables (NIH, 1985). Its choice was based primarily on the much greater comparability of absolute risks than relative risks for breast cancer in U.S. and Japanese exposed women.

An alternative approach is to assume that multiplicative or relative risks are comparable, and to apply excess relative risks obtained from the A-bomb survivors directly to baseline risks for the U.S. population. This alternative, which is referred to in this report as the "multiplicative transportation model", was used in NUREG/CR-4214 for calculating the upper bound estimate for lung cancer risks, and was used for all BEIR V estimates. UNSCEAR 88 used the 1982 Japanese life table population as its reference population, but used the multiplicative model to transport from the A-bomb survivor cohort to a modern population. The

multiplicative transportation model has advantages in that it is less affected by incomplete ascertainment of deaths, and by differences in the fatality of cancers in populations in different countries and across time.

The choice between additive and multiplicative transportation models is important in determining risk estimates for cancer types, such as lung cancer, where baseline rates for the Japanese and U.S. populations differ greatly. Land and Sinclair (1991) present lifetime risk estimates for several types of cancer, obtained by using the two approaches in extrapolating A-bomb survivor based estimates to the populations of the U.S., Japan, Puerto Rico, United Kingdom, and China. Age-specific risk coefficients from the A-bomb survivor Life Span Study were applied to cancer mortality rates from the respective populations to obtain these estimates. The average of the lifetime risk estimates for U.S. males and females are given in Table 3.10. With the exception of cancers of the esophagus and stomach, for which baseline rates are much higher in Japan than in the U.S., the additive transportation model results in lower lifetime risks.

Table 3.10

Comparison of lifetime risk estimates obtained using the multiplicative and additive transportation models in applying Japanese A-bomb survivor risk estimates to a U.S. population^a

Cancer type	<u>Multiplicative model</u> (Deaths per 10⁴ Gy)	<u>Additive model</u>	<u>Ratio</u> (additive/multiplicative)
Leukemia	116	90	0.8
Esophagus	18	22	1.2
Stomach	38	277	7.3
Colon	412	160	0.4
Gastrointestinal ^b	469	460	1.0
Lung	227	105	0.5
Breast ^c	122	32	0.3
Ovary ^c	50	22	0.4
Bladder	74	40	0.5
Remainder	370	260	0.7
Other ^d	494	322	0.7
Total	1428	1009	0.7

^a Obtained by averaging risk for U.S. males and females presented by Land and Sinclair (1991), Table 4.

^b Obtained by summing estimates for esophagus, stomach, and colon.

^c These estimates apply to the entire population and are one-half the risks for females.

^d Obtained by summing estimates for ovary, bladder and remainder.

There is considerable uncertainty regarding the correct choice for transporting risks from one country to another. The best available data for evaluating this choice are those on breast cancer risks from studies in Japan, the United States, and Canada. Although analyses presented in BEIR V indicate that excess relative risks were more comparable across countries than absolute risks, apparently the A-bomb survivor data used for these analyses were incorrect. Analyses based on correct data indicate that relative risks are not comparable between Japanese and Caucasian women, but that there is little evidence for a difference in absolute risks^a. This is in agreement with an earlier analysis by Land *et al.* (1980). Data on other cancer types for evaluating this issue are limited, but the lung cancer excess relative risk estimate of 0.13 per Gy, based on the ankylosing spondylitis patients in Great Britain (UNSCEAR 88), is much lower than the estimate of 0.61, based on the A-bomb survivors (Shimizu *et al.*, 1990). This comparison also suggests that the multiplicative transportation model is not entirely appropriate.

Leukemia is an interesting disease with regard to the transportation issue. Fatality from this disease has changed with time, and a multiplicative transportation model will better account for this. Also leukemia risks depend on the type of leukemia, with no identified risk for chronic lymphatic leukemia. This form of leukemia is apparently very rare in Japan, but would constitute a major fraction of the baseline risks used in applying the leukemia model to U.S. rates, especially for older ages at risk.

3.3.4 Incidence Versus Mortality

BEIR V provides models for estimating both breast cancer incidence and thyroid cancer incidence, and these models were based on analyses of incidence data for the two types of cancer. However, the lifetime risk estimates based on these models are not presented in the report. UNSCEAR 88 is also restricted to mortality estimates. Thus, for estimating cancer incidence, the earlier approach is recommended. This approach makes use of the ratio of U.S. incidence and mortality rates, and is described in Section 3.3.4 of NUREG/CR-4214.

3.3.5 Age at Exposure

For most cancer types, larger risk coefficients were used in calculating upper bound estimates in NUREG/CR-4214 for those exposed under age 20 than those exposed over age 20. Non-age-specific risk estimates were generally used for obtaining central and lower bound estimates.

UNSCEAR 88 used non-age-specific risk coefficients for specific sites, and used both approaches for estimating risks from leukemia and for cancers other than leukemia (Table 3.3). BEIR V incorporated age at exposure effects into all models except that for respiratory cancer. A comparison of the risk coefficients used for females exposed at ages 15, 30 and 45 is shown in Table 3.11. For models incorporating time after exposure effects as well, the estimates are for 20 years following exposure. Except for leukemia, the ratios of coefficients for

^aDale Preston, personal correspondence. Although these revised findings have important implications for the choice of projection models, they probably did not greatly affect the BEIR V breast cancer risk estimates. Dr. Preston has indicated that because, with the data used in BEIR V analyses, relative risks for breast cancer in the three countries were very similar, the BEIR V breast cancer risk estimates should remain appropriate for the U.S. population.

Table 3.11

BEIR V excess relative risk coefficients (per Gy) for females exposed at ages 15, 30, and 45

	Time after exposure (years)	Age at exposure (years)		
		15	30	45
Leukemia	10	32.1	2.59	2.59
Leukemia	20	2.63	2.59	2.59
Breast	20	4.87	0.48	0.19
Lung	20	1.29	1.29	1.29
Digestive	10 +	1.41	0.52	0.19
Other	10 +	0.97	0.48	0.24

different exposure ages do not depend on sex or time after exposure. For leukemia, estimates are shown for both 10 and 20 years after exposure. It is evident that the BEIR V models incorporate strong age at exposure effects, which tend to yield large risk estimates for those exposed early in life.

The BEIR V Committee notes that there was no need for an age at exposure adjustment for respiratory cancer, and that when such an effect was estimated, it was close to zero, so that the lifetime risk estimates were not influenced by its inclusion. This is surprising in view of age-specific estimates presented by Preston *et al.* (1987), which indicate that risks of lung cancer for those exposed under age 20 were 5 times the risks for those exposed over age 20. The examination of age at exposure effects for several types of cancer by Preston *et al.* generally indicates that for cancers other than leukemia, the modifying effect of age at exposure is similar for cancers of different types. More recent analyses by Shimizu *et al.* (1990) also indicate much higher relative risks for those exposed early in life.

3.3.6 Sex

Most NUREG/CR-4214 estimates were based on a population including both males and females, although recommendations were given for obtaining sex-specific estimates. UNSCEAR 88 estimates are also intended to apply to a population of both sexes. BEIR V provides separate estimates for males and females, and the BEIR V Committee analysed the dependence of the excess relative risk on sex. For leukemia, and other cancers, the excess relative risk was judged not to depend on sex. For respiratory cancer, the relative risk for females was estimated to be about 2 times that for males. For digestive cancers, the relative risk for females

was estimated to be about 1.7 times that for males. For respiratory and digestive cancers, baseline risks are lower for females than for males, and the difference in the relative risk estimates obtained for the two sexes may indicate that additive rather than relative risks are more comparable between the two sexes.

BEIR V lifetime risks were obtained using the multiplicative transportation model applied separately to the two sexes. If the ratio of baseline risks for females and males in the 1980 U.S. population were approximately the same as the male/female ratio of estimated excess relative risks, then the lifetime risks would be expected to be approximately equal. That they are not indicates that these ratios are probably not equal. Also, females have somewhat higher lifetime risks simply because of their longer average lifespan.

Table 3.12 shows the ratios of male and female lifetime risks based on NUREG/CR-4214 recommendations and on the BEIR V estimates. Because of the uncertainty in extrapolating risks for the two sexes, it is not thought necessary to revise the recommendations regarding sex-specific estimates given in NUREG/CR-4214.

Table 3.12

Ratio of lifetime risks for males relative to females

	NUREG/CR-4214 recommendations	BEIR V
Leukemia	1.5	1.38
Respiratory	1.0	1.27
Digestive	1.0	0.59
Other	1.0	1.36
Thyroid	2.0	3.0 ^a

^a Lifetime risks are not presented, but the ratio of the additive coefficients for males and females is about 3.

3.3.7 Revised A-bomb Survivor Dosimetry and the Effect on Risk Coefficients

The absolute and relative risk coefficients used to derive lifetime risk estimates for NUREG/CR-4214 were summarized in Table 3.2 of that report. The Japanese A-bomb survivor data played a strong role in determining the estimates for all cancer types except breast and thyroid. These were based on T65D dose estimates, which have now been replaced with DS86 dose estimates. In this section, we consider the modification of risk coefficients resulting from revised dosimetry.

The effects of the new dosimetry are discussed extensively in two reports. Preston and Pierce (1987) compared risk coefficients for leukemia and for all cancer except leukemia based on the two dosimetries. Estimates based on shielded kerma and on organ doses were evaluated. These latter doses were calculated using average body transmission/organ absorption factors as individually calculated organ doses were not available at the time. Because DS86 dose estimates were not calculated for some survivors with T65D estimates, the effect of restricting analyses to the subcohort with DS86 doses was also considered. Results based on analyses restricted to survivors with doses less than 4 Gy were also presented. Recall that BEIR V analyses were restricted to this latter group.

Shimizu *et al.* (1987) also compared results for T65D and DS86 dosimetries, primarily for the subcohort with DS86 doses. Their analyses were based on individually calculated organ doses, which reflected posture and orientation of individual survivors. Risk estimates for several different cancer types were compared.

Both reports note that the ratio of estimates obtained from the two dosimetries is different for estimates based on kerma than for estimates based on organ doses. Under DS86 dosimetry, kerma doses are generally lower than under T65D dosimetry, but more of the dose is transmitted and absorbed. For some organs, these changes tend to cancel each other. Because of the small contribution of neutron dose in the DS86 dosimetry, risk estimates based on these revised doses do not depend strongly on the assumed RBE (radiobiological effect). By contrast, risk estimates based on the old dosimetry were strongly dependent on the RBE, and hence comparisons of estimates based on the two dosimetry systems also depend on the RBE.

Table 3.13, reproduced from Preston and Pierce (1987), shows excess relative risk coefficients for cancers other than leukemia and average excess risks (absolute risk coefficients) for leukemia. The T65D estimates were based on the full cohort, while the DS86 estimates were based on the subcohort with DS86 doses.

Table 3.13 (from Preston and Pierce, 1987)

Leukemia and cancers other than leukemia, organ dose equivalent:
estimates of risk for selected values of the neutron RBE

Neutron RBE	Cancers other than leukemia			Leukemia		
	Excess relative risk risk per sievert			Average excess risk per 10 ⁴ person-year sievert		
	T65D	DS86	DS86 <4 Gy	T65D	DS86	DS86 <4 Gy
1	0.72	0.60	0.70	2.92	3.23	3.46
5	0.60	0.58	0.68	2.26	3.09	3.31
10	0.50	0.56	0.66	1.75	2.91	3.15
20	0.36	0.53	0.62	1.21	2.62	2.86
30	0.28	0.49	0.59	0.93	2.37	2.62

For cancers other than leukemia, estimates presented in NUREG/CR-4214, and also estimates for BEIR III, were generally obtained from the full cohort applying a neutron RBE of about 10. The risk coefficients used in UNSCEAR 88 calculations were based on an RBE of 1 and used the entire DS86 subcohort. Thus, the modification in UNSCEAR risk coefficients resulting from changes in the treatment of dosimetry can be estimated as $0.60/0.50 = 1.20$, or about a 20% increase. Comparable calculations from Shimizu *et al.* (1987), based only on the subcohort with DS86 doses for the denominator, and based on absolute risk coefficients, yielded a ratio of 1.12. BEIR V analyses were based on an RBE of 20 and excluded survivors with doses greater than 4 Gy. Thus, in this case, the relevant ratio for comparing with BEIR III estimates based on an RBE of about 10 is $0.62/0.50 = 1.24$.

For leukemia, the risk coefficient used in NUREG/CR-4214 was the linear coefficient given in BEIR III, and was obtained from analyses of Leukemia Registry Cases for the period 1950-71. The fitted RBE from which this coefficient was obtained was apparently 11.3 as given in equation V-11 on p. 188 of BEIR III. The interpolated T65D estimate from Table 3.13 based on an RBE of 11.3 is 1.68. It is also noted that the fitted RBE for the linear-quadratic coefficients, also presented in BEIR III, was 27.8, and the interpolated T65D estimate for this RBE from Table 3.13 is 0.99.

The UNSCEAR 88 estimate for leukemia was based on an RBE of 1 using the full DS86 cohort, and thus the change in coefficients resulting from dosimetry changes can be estimated as $3.23/1.68 = 1.92$. For BEIR V, estimates were based on an RBE of 20 with estimated doses exceeding 4 Gy excluded yielding a ratio 1.70. In Section 3.4.1, another approach to determining this latter ratio yields almost exactly the same value.

3.3.8 Method of Calculating Lifetime Risks

The method used in NUREG/CR-4214 for calculating lifetime risks is very similar to that used in UNSCEAR 88. BEIR V uses a different approach in that deaths from radiation-induced cancers in persons who would eventually develop cancer later in life are not counted. The number of excess cancers estimated by the BEIR V approach is about 0.8 times the number of cancers estimated by the approach used in NUREG/CR-4214 and UNSCEAR.

Neither approach is incorrect; it is simply a question of what one wishes to count. BEIR V counts the number of persons who would have died of cancer and would not have died of cancer without radiation exposure, while NUREG/CR-4214 and UNSCEAR count the number of persons who would have died earlier than they would have without radiation exposure.

No change in the method for calculating lifetime risks is recommended. A cancer that results in life-shortening has a detrimental effect even if the person would have died later from cancer without radiation exposure. It may, however, be more appropriate to label the deaths counted as "premature" deaths rather than "excess" deaths. Because of the different counting methods, if BEIR V and NUREG/CR-4214 were based on exactly the same assumptions, one would expect NUREG/CR-4214 estimates to be about 25% higher than BEIR V estimates. In evaluating whether modifications are needed in NUREG/CR-4214 estimates, this difference is considered.

It is also noted that NUREG/CR-4214 and BEIR V differ with respect to the age distribution that is assumed for the exposed population. BEIR V uses a stationary lifetable population for this purpose, while NUREG/CR-4214 uses the 1978 United States population. Because the 1978 population has a higher proportion of persons at young ages than a lifetable population, the NUREG/CR-4214 calculations give greater weight to risks of those exposed early in life, and thus result in slightly higher overall lifetime risk estimates. For example, a non-age-specific relative risk projection for all cancers except leukemia based on the age distribution of the 1978 U.S. population would be about 8% higher than if a stationary lifetable population had been used. If an age-specific approach had been used, with the excess relative risk coefficient for those under age 20 assumed to be three times as large as those age 20 and older, the estimate based on the 1978 population would be about 12% higher. The age distribution of those who might be exposed in a future nuclear reactor accident is obviously unknown, and represents yet another uncertainty in the risk prediction process.

3.3.9 Uncertainty in Lifetime Risk Estimates

NUREG/CR-4214 provides both central estimates and upper and lower bound estimates. These bounds were intended to reflect alternative assumptions that were reasonably consistent with the data, and could not be assigned a level of confidence.

As discussed at the end of Section 3.2.2, BEIR V provides a more rigorous approach to assessing the uncertainty arising from sampling error in the estimated parameters for various models, and presents 90% confidence limits for leukemia and for all cancers other than leukemia in males and females (see Table 3.4). The 90% limits for leukemia cover a range of a factor between 2 and 3 above and below the estimate, while the limits for cancers other than leukemia cover a range of a factor of about 1.5. Because the BEIR V models include parameters to estimate the modifying effects of sex, age-at-exposure, and time since exposure, these confidence limits reflect, to some extent, uncertainty from these sources. However, as discussed in BEIR V, these confidence limits do not reflect uncertainty resulting from mis-specification of the model (including extrapolation beyond the follow-up period), and uncertainty from sources that could not be statistically modeled (such as transporting risks from a Japanese to a U.S. population, or the possible reduction in risks for exposure received at low dose rates). BEIR V provides a subjective assessment of uncertainty for selected sources that could not be evaluated statistically, but does not present intervals that reflect all sources in combination.

Although the uncertainty analyses presented in the BEIR V report are much more extensive than those in previous reports, it does not seem feasible to use the results presented to obtain limits for NUREG/CR-4214 lifetime risk estimates that have meaningful associated probabilities, and that adequately reflect all important sources of uncertainty. It is noted that estimates for specific categories of cancer, and for specific subgroups of the population would carry greater uncertainty than an overall cancer risk estimate for the total population.

To provide a more rigorous assessment of the uncertainty in NUREG/CR-4214 models would require detailed analyses that are beyond the scope of this report, and has not been attempted. The upper and lower limits continue to represent estimates based on alternative assumptions that are reasonably consistent with the available data. The range provided by the upper and lower limits primarily reflects uncertainty regarding the

appropriate DREF, but also reflects different transportation models (lung cancer), and different treatments of age-at-exposure (breast and lung cancer). Lower bounds are based on the absolute risk projection model, and thus reflect uncertainty in extrapolating risks over time.

3.4 Risk Estimates for Specific Types of Cancer

In this section, the models for specific cancer types are discussed, and recommendations regarding modification are made. In all cases, it is recommended that linear estimates be modified for low doses and dose-rates, as indicated in Section 3.3.1, to obtain central and lower bound estimates. The material below addresses the linear estimates that are to be used. Recommended modifications of these linear estimates are summarized in Section 3.5.

3.4.1 Leukemia

Leukemia risk estimates in NUREG/CR-4214 were based on an absolute risk model, and risks were assumed to continue 2 to 27 years from exposure. The linear risk coefficient of 2.24 per 10^4 PYGy (person-year-Gy) was the estimate provided in BEIR III derived from Japanese A-bomb survivor data for the period 1950-1971. This approach yielded a lifetime risk of 48 per 10^4 person-Gy, much lower than linear estimates in UNSCEAR 88 and in BEIR V.

Before making recommendations for modifying the earlier estimate, it is useful to consider estimates based on the calendar year-specific absolute risk coefficients provided by Shimizu *et al.* (1988). These coefficients were based on shielded kerma, but can be modified by 1.28, the ratio of the overall leukemia estimate based on bone marrow dose (2.94) to the overall estimate based on shielded kerma (2.30). The modified coefficients are presented in Table 3.14.

For the period 1950-70, the "average" risk coefficient can be estimated by the ratio of the total number of excess cases (66.5) to the total years for the period (17.9). This ratio is 3.72 per 10^4 PYGy, and is 1.66 times the earlier estimate of 2.24 per 10^4 PYGy. The earlier estimate had been based on approximately the same time period, so this increase can be attributed primarily to dosimetry modification. The discussion in Section 3.7 of NUREG/CR-4214 also indicated that dosimetry modifications would lead to about a 70% increase in DS86-based risk coefficients.

The risk coefficient for the later time period (1971-1985) can be estimated as $13.9/9.7 = 1.43$ per 10^4 PY Gy. Earlier estimates were based on the period 2-27 years following exposure, but increased follow-up indicates that leukemia risks persist, although at lower levels. The 13.9 additional deaths in the period 1971-85 provide a total that is about 20% higher than an estimate based only on deaths occurring in the earlier period. Thus, the combination of revised dosimetry, and the persistence of risks beyond 27 years after exposure increase risks by about 1.7×1.2 , a factor of about two.

Table 3.14

Lifetime risk estimates for leukemia based on calendar year-specific risk coefficients from the Japanese A-bomb survivor life span study

Calendar year period	Excess risk per 10 ⁴ PYGy ^a	Time after exposure (years)	Years lived in interval ^b	Excess leukemia deaths
1950-55	4.61	4-10	5.53	25.5
1956-60	5.50	11-15	4.39	24.1
1961-65	2.18	16-20	4.12	9.0
1966-70	2.05	21-25	3.84	7.9
1971-75	1.41	26-30	3.54	5.0
1976-80	0.90	31-35	3.24	2.9
1981-85	2.05	36-40	2.92	6.0
Total		4-40	27.58	80.4
Total 1950-70		4-25	17.88	66.5
Total 1971-85		26-40	9.70	13.9

^a Obtained by modifying risk coefficients in Shimizu *et al.* (1988), Appendix Table 5, by the factor 1.28.

^b Calculated as described in Section 3.7 of NUREG/CR-4214.

It is recommended that the linear risk coefficient for leukemia be increased by a factor of 2, from 2.24 to 4.5 per 10⁴ PYGy and applied over the same period, 2-27 years following exposure, as previously. In fact, some of the risk would occur later than 27 years, and more of the risk would occur in the early part of the 2-27 year period than in the later part of the period. However, these two simplifications should tend to compensate one another for the purpose of calculating loss in life expectancy.

The lifetime risk estimate obtained with this modification is 97 per 10⁴ person-Gy, very close to the linear estimates provided by UNSCEAR 88, but about a factor of 2 lower than the BEIR V linear estimate.

It is not entirely clear why the BEIR V estimate is so large. By the arguments above, dosimetry revisions and extension of the follow-up period should account only for about a factor of 2 increase over the linear estimate of 48 provided by NUREG/CR-4214 and by BEIR III. The remainder of the increase apparently results

because of the multiplicative model used to transport age-at-exposure and time-after-exposure specific relative risks to the U.S. population. The inclusion of chronic lymphatic leukemia in the U.S. baseline risks may be a part of the reason for the high linear lifetime risk estimate obtained in BEIR V.

As noted in NUREG/CR-4214, because the fatality of leukemia has changed with time (particularly childhood acute lymphatic leukemia), the model used may overestimate the number of deaths from leukemia, and may be more appropriate as an estimate of the leukemia incidence, including non-fatal cases.

3.4.2 Bone Cancer

The BEIR V Committee suggests a lifetime risk estimate for bone cancer due to protracted alpha irradiation of 200 per 10^4 person-Gy. This estimate was obtained from follow-up studies of persons with elevated body burdens of ^{224}Ra . If a neutron RBE of 20 is assumed, this yields a lifetime risk estimate of 10 per 10^4 person-Gy for exposure to low LET radiation at low doses and dose rates. Assuming a DDREF of 2, this would yield an upper bound linear estimate of 20 per 10^4 person-Gy, a factor of 10 higher than the linear estimate of 2.1 per 10^4 person-Gy given in NUREG/CR-4214. The BEIR V estimate was taken from the BEIR IV report (NAS/NRC, 1988). The large increase in the estimate over that used in BEIR III, which was the basis of the NUREG/CR-4214 estimate, seems to result from the use of average skeletal dose by BEIR V, whereas the BEIR III estimate was based on endosteal dose. The BEIR IV calculations, based on work of Schlenker and Smith (1986), indicates that the approach used by BEIR III in calculating the endosteal dose probably resulted in underestimating risks by a factor of 2 or 3. UNSCEAR 88 judged the data inadequate for obtaining a quantitative risk coefficient for bone cancer.

ICRP 60 expresses a preference for an alternative estimate, primarily because the preferred BEIR V estimate does not account for competing risks. ICRP 60's preferred estimate is 133 per 10^4 person-Gy for bone cancer incidence, and a reduced estimate of 93 per 10^4 for bone cancer mortality. If reduced by an RBE of 20, the incidence and mortality estimates would be 6.7 and 4.7 per 10^4 person-Gy at low doses and dose rates, respectively. With a DDREF of 2, the upper bound linear estimates for incidence and mortality would be 13.3 and 9.3 per 10^4 person-Gy. The mortality estimate is about 4 times NUREG/CR-4214 estimates. BEIR IV discusses several analyses of the human data on ^{224}Ra , based on different methodologies and yielding different lifetime risk estimates.

Based on the discussion presented in ICRP 60, it is recommended that the earlier NUREG/CR-4214 coefficient for bone cancer mortality be increased by a factor of 4, from 0.1 to 0.4 deaths per 10^4 PYGy, yielding a lifetime linear risk estimate of about 9 per 10^4 person-Gy.

3.4.3 Breast Cancer

Breast cancer risk estimates in NUREG/CR-4214 were based on data from two U.S. studies of women treated with X-rays for mastitis and with X-ray fluoroscopy for tuberculosis. From Table 3.8, it can be seen that the NUREG/CR-4214 estimates are considerably higher than those provided by UNSCEAR 88 or by BEIR V.

The UNSCEAR 88 estimates were based on a Japanese reference population for which breast cancer rates are low, and thus it is not surprising that these estimates are lower than those given in NUREG/CR-4214.

The BEIR V Committee estimated the level of risk from breast cancer using mortality data from the A-bomb survivor Life Span Study and mortality data from a study of Canadian women who were treated with fluoroscopy for tuberculosis. The two U.S. studies used for NUREG/CR-4214 estimates were also considered in determining models for cancer mortality and incidence. Nova Scotia women had much higher risks than the remainder of the Canadian cohort, and these women were excluded in determining the level of risk. BEIR V provides separate breast cancer models for incidence and mortality, but lifetime risk estimates are presented only for mortality.

The BEIR V model for breast cancer includes strong dependencies on both age at exposure and time after exposure (see Figure 3.1), and this is the reason that BEIR V predicts lower risks than NUREG/CR-4214. These effects lead to very low relative risk coefficients for older ages at risk when breast cancer rates are high.

The data used by the BEIR V Committee were those described by Shore *et al.* (1986), Hrubec *et al.* (1989), Miller *et al.* (1989), and Shimizu *et al.* (1990). The first two papers present updated analyses of New York mastitis patients and the Massachusetts tuberculosis patients used in determining risk coefficients in NUREG/CR-4214. The excess relative risk coefficient from the New York study was 0.43 per Gy, but 0.58 per Gy when women with doses exceeding 7 Gy were excluded. The excess relative risk coefficient from the Massachusetts study was 0.73 per Gy. Neither study found evidence of a decline in the relative risk with time, but the Massachusetts study notes a decrease in risk with age at exposure. The NUREG/CR-4214 overall excess relative risk coefficient, obtained from earlier analyses of these two cohorts, was 0.45 per Gy. Thus, it is clear that increased follow-up of these cohorts has not reduced risk coefficients over those based on the follow-up period used in determining the NUREG/CR-4214 estimate.

Miller *et al.* (1989) report on the large study of Canadian women who were treated with fluoroscopy for tuberculosis. The overall excess relative risk coefficient for the non-Nova Scotia women was 0.53 per Gy, similar to the U.S. studies. The study provided clear evidence of a decline in the excess relative risk with age at exposure, with estimates of 3.46, 0.77, 0.25, and 0.10 per Gy for women exposed at ages 10-14, 15-24, 25-34, and ≥ 35 , respectively. The relative risk after 35 years of follow-up was decreased over earlier periods, but not significantly so. The A-bomb survivor Life Span Study yielded an estimated excess relative risk of 1.21 per Gy (Shimizu *et al.*, 1990), larger than the U.S. and Canadian studies (see Section 3.3.3).

Unlike estimates for most other types of cancer, central estimates for breast cancer in NUREG/CR-4214 were not modified by reduction factors to account for low doses and dose-rates. No change in the application of reduction factors for breast cancer is recommended. With the exception of very high risks in the Nova Scotia women (with very high doses), the BEIR V analyses, and analyses presented in papers describing specific cohorts, found no evidence of non-linearity for breast cancer. Also, the fractionated doses in the fluoroscopy series were not found to reduce risks over more acute exposures such as those received by the New York mastitis patients. However, none of the reports (UNSCEAR 88, BEIR V, ICRP 60) indicate that breast cancer should be an exception to the general recommendation that reduction factors should be applied.

Certain modifications of the NUREG/CR-4214 breast cancer model are recommended. The recommended coefficients for calculating upper bound estimates are 1.0 per Gy for women exposed under age 20 and 0.4 per Gy for women exposed over age 20. These choices are very similar to those used previously.

The recommended excess relative risk coefficients for calculating the central estimates are as follows: 0.7 per Gy for women exposed under age 20, 0.3 for women exposed between 20 and 40, and 0.1 for women exposed over age 40. The linear lifetime risk estimate based on these coefficients is 108 deaths per 10^4 person-Gy for females, or 54 per 10^4 person-Gy for a population of both sexes, about 54% higher than the BEIR V estimate, and slightly lower than the central estimate of 60 per 10^4 person-Gy given in NUREG/CR-4214. The earlier NUREG/CR-4214 estimate was based on a non-age-specific excess relative risk coefficient of 0.45 per Gy.

The revised central estimate is only slightly lower than the previous NUREG/CR-4214 estimate, but provides for a different distribution of deaths by age at exposure. Because of the strong evidence for a decrease in relative risk with increasing age at exposure, it does not seem appropriate to continue using a non-age-specific model. It is possible that because of attenuation of risk with time after exposure, the NUREG/CR-4214 linear models could overestimate breast cancer risks, but the evidence for such reduction did not seem strong enough to reduce central estimates to the extent of the BEIR V breast cancer model.

The NUREG/CR-4214 lower bound linear risk estimate was based on an absolute risk model, and no change is recommended. Absolute risk coefficients presented in the reports discussed above are reasonably comparable to those used in NUREG/CR-4214.

3.4.4 Lung Cancer

Both BEIR V and UNSCEAR 88 provide higher linear lung cancer risk estimates than those derived from the NUREG/CR-4214 models. This can be attributed to increases in the Japanese A-bomb survivor risk coefficients resulting from revised dosimetry and increased follow-up, and to the use of the multiplicative transportation model for obtaining risks for the U.S. population (BEIR V). This increase is slightly mitigated by the decrease in risks with time after exposure used in the preferred BEIR V model.

In NUREG/CR-4214, the upper bound estimate was based on a multiplicative transportation model using an excess relative risk coefficient of 0.37 per Gy; this coefficient was obtained directly from A-bomb survivor data from the period 1950-82 (Kato and Schull, 1982). Although the preferred BEIR V model includes a decrease with time after exposure, the excess relative risk coefficients from an alternative model without such a decrease were also presented, and were estimated to be 0.42 per Gy for males and 0.64 per Gy for females, yielding an average of 0.53 per Gy. The increase in risk coefficients (from 0.37 per Gy) is due to changes in dosimetry (see Section 3.3.7), increased follow-up, and possibly also in differences in methods used by Kato and Schull and by the BEIR V Committee.

As discussed in Section 3.3.3, there is uncertainty regarding the appropriate method for transporting risks from the A-bomb survivor cohort to the U.S. population. The much lower risk estimate of 0.13 per Gy for the ankylosing spondylitics (UNSCEAR 88, p. 523) suggests that the additive transportation model may be more

appropriate, and this was the choice used for central estimates in NUREG/CR-4214. Results of calculations based on the two transportation methods given in Table 3.10 indicate that the additive transportation model results in lifetime risk estimates that are about 50% of those obtained using the multiplicative transportation model.

Data on miners exposed to alpha radiation from radon and radon progeny also merit consideration. BEIR IV (NAS/NRC, 1988) presents combined analyses of data from miners in the U.S., Sweden, and Canada. The BEIR IV model included a decline in risk with time, but the BEIR IV Committee also fitted a constant relative risk model and obtained an excess relative risk coefficient of about 1.4% per working level month (WLM). BEIR IV suggests a factor of 3 to 10 for converting WLM to mGy. These factors in combination with an assumed RBE of 10 (see discussion in Section 3.4.2) yield risk estimates for low-LET radiation (at high doses and dose rates) ranging from 0.14 to 0.47, compared to the BEIR V estimate of 0.42 per Gy for A-bomb survivor males. This range is consistent with either the additive or the multiplicative transportation model.

Differences in lung cancer rates between countries may be largely a reflection of differences in smoking habits. Thus, a multiplicative interaction of radiation and smoking would support the use of the multiplicative transportation model, while an additive interaction would support the additive transportation model. BEIR IV presents analyses of the interaction of radiation and smoking using data from Colorado miners, from New Mexico miners, and from A-bomb survivors. Analyses of data from the Japanese A-bomb survivors suggest an additive interaction, but are also consistent with a multiplicative interaction. However, analyses of lung cancer risks in miners indicate that a multiplicative model fit the data significantly better than an additive model.

BEIR V did not include an age at exposure effect in its respiratory cancer model, and indicated that such an effect was close to zero and would not have significantly modified the lifetime risk estimates. As discussed in Section 3.3.5, the age at exposure effect for lung cancer does not seem out of line with that provided in other reports, and it seems difficult to justify the use of age-specific coefficients for most other cancers, but not for lung cancer. The time after exposure effect was not statistically significant based on analyses of the A-bomb survivor data alone, and the decrease with follow-up time seen in the ankylosing spondylitis patients was part of the reason this effect was included in the BEIR V model. It is possible that changes in smoking habits could be responsible for this decline.

It is recommended that the relative risk coefficient of 0.37 per Gy previously used for obtaining upper bound estimates in Table 3.2 of NUREG/CR-4214 be changed to 0.5 per Gy. The 0.5 value is approximately the average of the male and female risk estimates presented in BEIR V (in a model without time since exposure effects), and results in increasing upper bound risks by a factor of $0.50/0.37 = 1.35$. A coefficient three times 0.5, or 1.5, should be used for those exposed under age 20, comparable to NUREG/CR-4214 where a coefficient three times 0.37 was used for those exposed early in life. These changes result in a upper bound lifetime risk estimate of 331 deaths per 10^4 person-Gy.

For obtaining central estimates, the risk coefficient of 0.18 should be replaced with the coefficient 0.3 per Gy. This is obtained by reducing the A-bomb survivor based coefficient of 0.53 by about 50%, the ratio of estimates

obtained using additive and multiplicative transportation from the A-bomb survivors to a U.S. population (see Table 3.10). It is recommended that this risk coefficient be applied for those exposed over age 20, with a coefficient of 0.6 applied for those exposed under age 20. Although it might be argued that basing the central estimate on additive transportation may result in underestimation, the use of an age-specific model and a model that does not include a decrease in risk with time since exposure may result in overestimation of risks. The model chosen seems a reasonable compromise, and these changes result in a linear central estimate of 155 deaths per 10^4 person-Gy.

The NUREG/CR-4214 lower bound estimate was based on an additive extrapolation model, with estimates obtained from the Japanese A-bomb survivors. It is recommended that the earlier risk coefficient of 2.0 be increased to 2.5 per 10^4 PYGy to account for revised A-bomb dosimetry (see Section 3.3.7). The absolute risk coefficient for cancer incidence should be changed from 2.2 to 2.7 per 10^4 PYGy.

These models do not include the decline in risks with time after exposure that were included in the BEIR V model. Some insight regarding the comparison of respiratory risks with and without a time after exposure effect can be obtained by comparing the BEIR V risk estimate of 170 deaths per 10^4 person-Gy (averaged over males and females) with an estimate of 189 per 10^4 person-Gy, based on an alternative model without a time after exposure effect.

Although the time effect does not have a large effect on the overall risk estimate, it has a very large effect on risks for those who are very young at exposure. For those exposed at age 5, the BEIR V preferred model yields a lifetime risk of 33 per 10^4 person-Gy as compared with a risk of 238 per 10^4 person-Gy for the BEIR V alternative model without the time after exposure adjustment. The combination of using a non-age at exposure-specific model and the decline in risks with time since exposure results in very low risks for those exposed early in life. Although these low risks are possible, they do not seem the best choice for a central estimate. The linear central estimate for those exposed under age 10, based on the revised NUREG/CR-4214 model, is 265 per 10^4 person-Gy.

3.4.5 Gastrointestinal Cancer

The NUREG/CR-4214 model for gastrointestinal cancer was based primarily on the A-bomb survivor studies with some consideration of estimates based on ankylosing spondylitis patients. The general approach was to add up absolute risk estimates for specific sites, and this could possibly have led to overestimation as negative estimates were not generally considered (or even presented in reports providing source estimates).

BEIR V analyses of digestive cancer demonstrated a strong dependence of risks on age at exposure, with the excess relative risk coefficient for those exposed under age 25 being about 7 times that for those exposed over age 35 (see Table 3.11). The model provides a lifetime estimate of 230 per 10^4 Gy, which would be about 25% higher, or 288 per 10^4 person-Gy, if the counting method recommended for NUREG/CR-4214 had been applied. This is 88% of the age-specific NUREG/CR-4214 estimate of 329 per 10^4 person-Gy. The multiplicative transportation model used in BEIR V results in risks that are about 80% of the risks that would

have been obtained using the additive transportation model (see Table 3.10), and this may be part of the explanation for the difference in the two models. There is little available evidence to determine which of these transportation methods is more appropriate.

The average of male and female BEIR V excess relative risk coefficients for those exposed under age 25, at age 30, and at age 35 and over are 1.1, 0.4, and 0.15 per Gy, respectively. The coefficients used in the NUREG/CR-4214 model for upper bound linear estimates were 1.17 and 0.39, respectively, for those exposed under age 20, and at age 20 and over. It is recommended that coefficients of 1.2 and 0.4 be used for those exposed under and over age 20, essentially the same as those used previously. It is also recommended that age-specific risk estimates be used for both upper and central limits.

These choices lead to a linear lifetime risk estimate of 337 per 10^4 person-Gy, which is about 47% above the estimate provided by the BEIR V model, or about 17% higher if the counting method recommended by NUREG/CR-4214 had been applied in BEIR V. It is noted that the A-bomb survivor digestive cancer data, used by the BEIR V Committee, were dominated by stomach cancer, where the excess relative risk is lower than for colon cancer (Shimizu *et al.* 1990), the digestive cancer which predominates in the U.S. It is also noted that direct transportation of risks for cancers of the esophagus, stomach, and colon yields a total that is higher than either the BEIR V or the revised NUREG/CR-4214 estimates (see Table 3.10).

The NUREG/CR-4214 lower bound estimate for fatal gastrointestinal cancers was based on an absolute risk projection model, using a risk coefficient of 2.7 per 10^4 PYGy. Shimizu *et al.* (1990) present an absolute risk coefficient of 3.39 per 10^4 PYGy based on shielded kerma. Shimizu *et al.* also present risk estimates for stomach cancer of 2.42 per 10^4 PYGy based on dose to the stomach, and of 2.07 based on shielded kerma. Using the ratio of the two stomach cancer estimates, the risk coefficient for all digestive cancers, based on dose to the stomach, would be about 4 per 10^4 PYGy. It is recommended that the coefficient for calculating the lower bound estimate for mortality from gastrointestinal cancers be increased from 2.7 to 4.0 per 10^4 PYGy. Because absolute risk coefficients tend to increase as the population ages, this change comes about in part because of increased follow-up of the A-bomb survivor population. The coefficient for calculating cancer incidence should be increased in the same proportion, from 4.6 to 6.8 per 10^4 PYGy.

NUREG/CR-4214 also provides a distribution of risks by specific cancer types, and this distribution was based on the additive risk coefficients. The proportional distribution was as indicated below.

Esophagus	0.074	Rectum	0.037
Stomach	0.444	Pancreas	0.074
Colon	0.185	Other GI	0.185

BEIR V presents estimates only for digestive cancers as a group, although the evidence for a radiation-association for specific types of cancer is reviewed. UNSCEAR 88 provides estimates only for cancers of the esophagus, stomach, and colon, and the estimates given in Tables 3.8 and 3.9 were obtained by summing these

three values. These were the only three digestive cancers shown to be statistically significant in the A-bomb survivors. ICRP 60 selects only cancers of the esophagus, stomach, colon, and liver for providing weighting factors.

Because stomach cancer is the predominant gastrointestinal cancer in Japan, while colon cancer is the predominant gastrointestinal cancer in the U.S., the choice of transportation model has a strong effect on the proportional allocations of different cancer types. From Table 3.10, the multiplicative transportation model would yield the proportions 0.038, 0.081, and 0.879 for cancers of the esophagus, stomach, and colon, respectively, while the additive transportation model would yield the respective proportions of 0.048, 0.602 and 0.348. The averages of these two values would be 0.043, 0.342, and 0.614.

Because the liver is an organ that may be selectively irradiated, it merits special attention. Neither the A-bomb survivor Life Span Study nor the ankylosing spondylitis study showed clear evidence of an association with radiation. However, follow-up studies of patients exposed to Thorotrast yield a lifetime risk estimate of 300 cancers per 10^4 person-Gy, and this estimate is cited in BEIR V, ICRP 60, and BEIR IV. With an RBE of 20, this is 15 liver cancers per 10^4 person-Gy for exposure to low-LET radiation at low doses and dose rates. With a DDREF of 2, the upper bound linear estimate would be 30 liver cancers per 10^4 person-Gy, or about 10% of the total of 337 cancers predicted using the age-specific linear model.

The following proportional allocation of digestive cancers is suggested.

Esophagus	0.05	Liver	0.10
Stomach	0.25	Other	0.10
Colon	0.50		

For the purpose of calculating dose, the "other" category is not appropriate so the allocation should be revised as 0.05 for esophagus, 0.30 for stomach, 0.55 for colon, and 0.10 for liver. If lifetime risk estimates for any of these specific cancer types are desired, it is suggested that the dose to the organ of interest be used to calculate the overall risk for all digestive cancers and then be reduced by the appropriate factor indicated above. It should however be recognized that risk estimates for specific organs carry especially large uncertainties.

3.4.6 Thyroid Cancer and Benign Thyroid Nodules

BEIR V provides a model for thyroid cancer risks, but does not present lifetime risk estimates. The model is based on the Israeli born portion of the Israel Tinea Study. Baseline thyroid cancer risks for this population would be required to use the model for calculating thyroid cancer risks. However, the additive risk coefficients presented for this cohort suggest that lifetime risks would be substantially higher than those based on the NUREG/CR-4214 model. BEIR V does not provide a model for thyroid nodules.

Both ICRP 60 and UNSCEAR 88 adopted the thyroid cancer risk estimates provided by NCRP (1985). The NUREG/CR-4214 was also taken from NCRP (1985). No modification of the thyroid disease models is recommended.

3.4.7 Skin Cancer

Neither BEIR V nor UNSCEAR 88 provide lifetime risk estimates for skin cancer. ICRP 60 recommends an estimate for fatal skin cancer of 2 per 10^4 person-Sv, obtained by reducing an incidence estimate of 980 skin cancers per 10^4 per person-Sv by a factor of 0.002. This incidence estimate is substantially higher than the NUREG/CR-4214 estimate of 67 per 10^4 person-Gy.

The basis for the ICRP 60 estimate is provided by Shore (1990) and in a report of the ICRP Task Group on the Skin (in progress). The estimate was obtained by combining risk estimates from several studies, considering the area of the body irradiated, and providing separate coefficients for those parts of the body expected to be exposed to ultraviolet radiation (UVR) (face, neck, dorsal aspect of the hands and arms), and those parts shielded from UVR (remainder of the body). Estimates using both absolute and relative risk projections over time are presented in ICRP 60, and yield respective lifetime risks of 230 and 980 skin cancers per 10^4 per person-Sv. The relative risk projection model was judged more appropriate, but may overestimate risks, especially in view of the fact that several of the studies contributing data involve persons exposed early in life. Although skin cancer data are inadequate to adequately investigate the role of age-at-exposure, data on many other types of cancer indicate that relative risks for those exposed early in life are usually larger than for those exposed in adulthood. The ICRP 60 risk estimates do not include a DDREF to reduce risks for low doses and dose rates.

The skin cancer risk estimate from NUREG/CR-4214 was based on an absolute risk projection model, and this is part of the reason that it is lower than the ICRP 60 recommended estimate. In addition, the absolute risk coefficient used was not adjusted to allow for the fact that in most studies providing data, only a fraction of the body skin was irradiated. Although the adjustment used by Shore in obtaining the ICRP 60 estimates is probably imprecise due to uncertainties in the skin area irradiated in various studies, such an adjustment is needed if estimates are to be based on average dose to the skin.

It is recommended that an approach similar to that used by ICRP 60 be adopted for the upper bound estimate. The relative risk projection model should be used, applying the excess relative risk coefficient of 0.5 per Gy to the average dose to UVR-exposed skin. The excess relative risk coefficient given by Shore for UVR-exposed skin is 0.58 per Gy, but is reduced by 0.9 because about 90% of all skin cancers occur on those parts of the body exposed to UVR. A comparably calculated risk estimate for UVR-shielded skin is 0.0005 per Gy, which is so small that its contribution could generally be ignored. In a reactor accident, it would be expected that most dose would be received by parts of the body that are also exposed to UVR.

Baseline rates are needed to apply this model. The rates used by the ICRP 60 are reproduced in Table 3.15, and were obtained from surveys conducted by Scotto *et al.* (1974, 1983) and by Fears and Scotto (1982). Applying the computational approach outlined in Section 3.7 of NUREG/CR-4214, the baseline or spontaneous risk is 1775 skin cancer cases per 10^4 population. These are distributed as 312, 373, 383, 283, and 423 for the respective age at exposure categories 0-9, 10-19, 20-29, 30-39, 40+. These values should be added to Table 3.12 in NUREG/CR-4214 for the purpose of calculating skin cancer risks. The upper bound estimate is thus $0.5 \times 1775 = 888$ cases per 10^4 person-Gy.

Table 3.15**Skin cancer rates per 1000 person-years^a**

Ages	Males	Females
0-4	0.2	0.2
5-9	0.3	0.3
10-14	0.5	0.5
15-19	0.9	2.1
20-24	7.1	6.5
25-29	20.9	22.5
30-34	41.9	40.0
35-39	92.3	70.2
40-44	177.5	122.1
45-49	286.0	194.5
50-54	421.8	258.3
55-59	600.2	334.9
60-64	786.7	402.0
65-69	1079.7	492.0
70-74	1286.1	634.5
75-79	1636.5	812.0
80-84	1889.7	907.2
85+	1773.2	955.6

^a Based on Scotto *et al.* (1974,1983) and Fears and Scotto (1982)

For central estimates, it is recommended that the upper bound be reduced by a DDREF of 2 as described in Section 3.3.1. Although the ICRP 60 did not reduce risks for protracted exposures, they indicate that such reduction is likely.

For the lower bound estimates, the absolute risk model is recommended, using the coefficient of 6.7 per 10⁴ PYGy, the coefficient given in ICRP 60 for UVR-exposed skin. The dose should be the average dose to UVR-exposed skin. This coefficient compares to a value of 2.0 per 10⁴ PYGy used in NUREG/CR-4214 and leads to a linear lifetime risk estimate of 218 per 10⁴ person-Gy. A DDREF of 4 should be applied to obtain lower bound estimates for low doses and dose rates.

3.4.8 Other Cancers

NUREG/CR-4214 estimates for other cancers were obtained through the somewhat arbitrary choice of an absolute risk coefficient of 1.5 per 10^4 PYGy. The BEIR V approach was based on analyses of other cancers in the Life Span Study cohort, and yielded estimates that were substantially higher than the NUREG/CR-4214 model.

A part of the reason for the high risk in males based on the BEIR V model may have been the inclusion of prostate cancer in the baseline risks used for calculating lifetime risks. This disease has particularly high mortality rates late in life. Because prostate cancer has not been clearly associated with radiation in epidemiologic studies, the appropriateness of including this disease is not clear. Neither NUREG/CR-4214 nor BEIR III included prostate cancers in calculating lifetime risks based on multiplicative projection models.

It is recommended that the risk estimate for those exposed under 20 be increased from 0.6 to 1.1, the average of the BEIR V risk estimates for males and females and for exposure at ages 5 and 15. The risk coefficient for those exposed over age 20 should be increased from 0.2 to 0.25. These values were chosen so that the BEIR V estimate for females (220 per 10^4 person-Gy) is 80% of the NUREG/CR-4214 life time risk based on the age-specific risk coefficients above. It is further recommended that the age at exposure-specific linear estimate be used for both upper bound and central estimates. BEIR V analyses of other cancers show a strong age at exposure effect.

It is also recommended that the absolute risk coefficient used for calculating the lower bound estimate for other cancer mortality be increased from 1.5 to 3.5 per 10^4 PYGy. Based on Shimizu *et al.* (1990), the sum of the kerma based absolute risk coefficients for cancer types other than leukemia, breast, digestive, and respiratory is 2.6 per 10^4 PYGy. If this is adjusted based on cancer types for which organ dose estimates are presented (ovary, urinary, and multiple myeloma), the result is about 3.5 per 10^4 PYGy. For other cancer incidence, the coefficient should be increased in the same proportion, from 2.9 to 6.8 per 10^4 PYGy.

It was previously suggested that doses to the bone marrow, kidney, urinary bladder, brain, uterus, and ovary be considered in making dose calculations for other cancers. The only modification of this suggestion is that the uterus be dropped as the evidence associating this cancer with radiation is equivocal. The Life Span Study provides evidence of statistically significant associations for multiple myeloma and cancers of the bladder and ovary, and these are the only specific sites considered in UNSCEAR 88 or in the ICRP 60 weighting factors. However, other studies have provided evidence for an association of radiation exposure with cancers of the brain and kidney (BEIR V).

It is difficult to obtain quantitative estimates of risks to specific organs within the other cancer group. However, using the averages of lifetime estimates based on multiplicative and additive transportation models from Table 3.10, the lifetime risk for bladder cancer is estimated as 57 per 10^4 person-Gy, while that for cancer of the ovary is estimated as 36 per 10^4 person-Gy. The UNSCEAR estimate for multiple myeloma, based on the multiplicative model for a Japanese population is 22 per 10^4 person-Gy. Thus, bladder cancer, ovarian cancer, and multiple myeloma can be estimated to constitute about 20%, 13%, and 8%, respectively, of the total other

cancer risk of 276 per 10^4 person-Gy. These proportions could be used in a manner similar to that suggested in Section 3.4.5 to obtain organ-specific estimates for these types of cancer, although the estimates would be highly uncertain. To obtain estimates of ovarian cancer for females, the 13% value would need to be doubled.

3.4.9 Cancers Resulting from *In Utero* Exposure

NUREG/CR-4214 provided a central estimate of 230 deaths from leukemia and other cancers per 10^4 person-Gy for persons exposed *in utero*. BEIR V cites an estimate of 200 to 250 excess cancer deaths per 10^4 person-Gy, and also notes that an analysis by Bithell and Stiller (1988) of data from the Oxford survey yields an estimate of 217 per 10^4 person-Gy. Yoshimoto et al (1988) report two cases of childhood cancers in those with high *in utero* A-bomb exposures, a finding that yields an upper bound on the risk estimate of 279 cases per 10^4 person-Gy, consistent with data from the Oxford survey. UNSCEAR 88 makes no new recommendations regarding risk estimates from *in utero* exposure, while ICRP 60 cites the estimate of 200 per 10^4 person-Gy from an earlier UNSCEAR report.

No modifications of the NUREG/CR-4214 model for *in utero* exposure are recommended.

3.5 Summary of Recommended Modifications to NUREG/CR-4214 Models

3.5.1 Modification of Reduction Factors for Low Doses and Dose Rates

For leukemia, bone cancer, lung cancer, skin cancer, and other cancers, linear estimates should be reduced by a DDREF to obtain central and lower bound estimates when the total dose is less than 0.2 Gy, and for higher doses when the dose rate is less than 0.1 Gy per hour. The DDREF to be applied for the central estimates is 2, and that for the lower bound estimates is 4. The DDREF of 4 should also be applied in obtaining lower bound estimates for breast cancer. The linear-quadratic functions indicated in NUREG/CR-4214 should not be applied.

3.5.2 Use of Age at Exposure-Specific Coefficients

The central estimates for breast cancer, lung cancer, gastrointestinal cancers, and other cancers should be based on the age-specific rather than on the non-age-specific estimates. Age-specific estimates were used in NUREG/CR-4214 for upper bound estimates for these cancer types.

3.5.3 Modifications in Risk Coefficients

Several changes in risk coefficients are recommended, and apply to both cancer mortality and cancer incidence. The reasons for these changes were discussed in Section 3.4, and the new coefficients are given below and summarized later in Tables 3.20 and 3.21.

The absolute risk coefficient for obtaining upper bound, central, and lower bound estimates for leukemia should be increased by a factor of 2, and that for bone cancer by a factor of 4. The modified linear risk coefficients are then 4.5 per 10^4 PYGy for leukemia and 0.4 per 10^4 PYGy for bone cancer.

The relative risk coefficients used to obtain the upper bound estimate for breast cancer in women should be 1.0 per Gy for those exposed under age 20, and 0.4 per Gy for those exposed at age 20 and over, very similar to those used previously. The excess relative risk coefficients used to obtain central estimates should be 0.7 per Gy for those exposed under age 20, 0.3 per Gy for those exposed between 20 and 40, and 0.1 per Gy for those exposed at age 40 and over. Previously, the coefficient 0.45 per Gy was used for all exposure ages.

The excess relative risk coefficients used to obtain the upper bound estimate for lung cancer should be increased from 1.11 to 1.5 per Gy for those exposed under age 20, and from 0.37 to 0.5 per Gy for those exposed at age 20 and over. The age-specific risk coefficients used to obtain the central estimate for lung cancer should be 0.6 per Gy for those exposed under age 20 and 0.3 per Gy for those exposed at age 20 and over, compared to the non-age-specific coefficient of 0.18 per Gy used previously. The absolute risk coefficient used to obtain the lower bound estimate for lung cancer mortality should be increased from 2.0 to 2.5. The absolute risk coefficient used to obtain the lower bound estimate for lung cancer incidence should be increased from 2.2 to 2.7.

The absolute risk coefficient used to obtain the lower bound estimate for fatal gastrointestinal cancer should be increased from 2.7 to 4.0 per 10^4 PYGy. The corresponding coefficient for calculating gastrointestinal cancer incidence should be increased from 4.6 to 6.8 per 10^4 PYGy.

The excess relative risk coefficients used to obtain the upper bound and central estimates for other cancer should be increased from 0.6 to 1.1 per Gy for those exposed under age 20, and from 0.2 to 0.25 per Gy for those exposed over age 20. The absolute risk coefficients used to obtain lower bounds should be increased from 1.5 to 3.6 per 10^4 PYGy for mortality and from 2.9 to 6.8 per 10^4 PYGy for incidence.

For skin cancer, the upper bound and central estimates should be based on a relative risk projection model, using a coefficient of 0.5 per Gy. The absolute risk coefficient for the lower bound estimate should be increased from 2.0 to 6.7 per 10^4 PYGy.

3.5.4 Comparison of Modified Estimates with BEIR V, UNSCEAR 88 and ICRP 60

Tables 3.8 and 3.9 present comparisons for linear estimates from NUREG/CR-4214 with estimates from BEIR V, UNSCEAR 88, and ICRP 60. Tables 3.16 and 3.17 show these same comparisons using NUREG/CR-4214 estimates as modified by the above recommendations. Table 3.18 shows a comparison of excess deaths in those exposed under 20 years of age for the modified NUREG/CR-4214 model and BEIR V. The BEIR V estimates in Table 3.17 were obtained from Table 3.5 as the average of estimates for males and females exposed at ages 5 and 15.

With the exception of lung cancer, the central estimates for the revised NUREG/CR-4214 model are slightly higher than BEIR V estimates, but should be so because of the different method of counting cancers. The NUREG/CR-4214 central estimate for breast cancer is substantially higher than either of the other two models, and the reasons for this are discussed in Section 3.4.3. The lower lung cancer risk estimate can be accounted for by the use of additive rather than multiplicative transportation from the Japanese A-bomb survivor study. The overall NUREG/CR-4214 central estimate for loss in life expectancy of 1.45 years per person-Gy is reasonably comparable to that provided by BEIR V. With the exception of lung cancer, NUREG/CR-4214 central estimates and BEIR V estimates for risks in those exposed under age 20 are also similar. The discrepancy in the lung cancer estimates is discussed in Section 3.4.4.

3.5.5 Tables Summarizing the New Model

Tables 3.19-3.22 are revised versions of Tables 3.1-3.3, and 3.5, respectively, from NUREG/CR-4214. These tables incorporate the recommended modifications.

Table 3.16

Linear lifetime risk estimates^a for fatal cancer. Excess deaths per 10⁴ person-Gy^b

Type of cancer	NUREG/CR-4214 with modifications recommended in Section 5			BEIR V ^c	UNSCEAR 88		ICRP 60
	Lower bound	Central	Upper bound		Multiplicative	Additive	
Leukemia	97	97	97	190 ^d	97 (100 ^e)	93 (100 ^e)	100
All cancers except leukemia	363	795	1027	695	610	360	900
Breast ^f	43	54	84	35	30	22	40
Lung	67	155	331	170	151	59	170
Gastrointestinal	135	336	336	230	239	131	480
Other	118	276	276	260	190	148	210
Total	347	918	1124	885	707 (1070 ^e)	452 (420 ^e)	1000

^a This table is presented for the purpose of comparing linear risk estimates, without consideration of modification by dose and dose rate reduction factors. For this reason, estimates have not been modified to account for low doses and dose rates. Thus, the NUREG/CR-4214 central estimates for most cancers in this table are a factor of 2 higher, the NUREG/CR-4214 lower bounds are a factor of 4 higher, the BEIR V estimate for leukemia is a factor of 2 higher, and all ICRP 60 estimates are a factor of 2 higher than modified estimates would be.

^b The NUREG/CR-4214 and BEIR V estimates are based on the U.S. population of all ages, the UNSCEAR 88 estimates are based on the population of Japan, and the ICRP 60 estimates are based on the populations of the U.S., United Kingdom, Japan, Puerto Rico, and China.

^c Unlike estimates from other reports, BEIR V estimates do not include radiation-induced cancer deaths in persons who would have died of cancer later, and would be about 25% higher had these deaths been included.

^d This is the linear estimate, and is double the linear-quadratic estimate provided by BEIR V for low doses and dose-rates.

^e These estimates were based on age-specific risk coefficients. The other UNSCEAR estimates presented were based on constant (age-averaged) risk coefficients.

^f These estimates apply to the entire population, and are one-half the risks for females.

Table 3.17

Linear lifetime risk estimates^a for fatal cancer. Years of life lost per person-Gy^b

Type of cancer	NUREG/CR-4214 with modifications recommended in Section 5			BEIR V ^c	UNSCEAR 88	
	Lower bound	Central	Upper bound		Multiplicative	Additive
Leukemia	0.34	0.34	0.34		0.22	0.30
All cancers except leukemia	0.84	1.10	1.42		0.73	0.91
Breast ^d	0.10	0.09	0.14		0.06	0.06
Lung	0.12	0.23	0.49		0.17	0.15
Gastrointestinal	0.33	0.41	0.41		0.28	0.33
Other	0.29	0.38	0.38		0.23	0.38
Total	1.18	1.45	1.76	1.33	0.95(1.40 ^e)	1.21(1.20 ^e)

^a This table is presented for the purpose of comparing linear risk estimates, without consideration of modification by dose and dose rate reduction factors. For this reason, estimates have not been modified to account for low doses and dose rates. Thus, the NUREG/CR-4214 central estimates for most cancers in this table are a factor of 2 higher, and the NUREG/CR-4214 lower bounds are a factor of 4 higher than the modified estimates would be.

^b The NUREG/CR-4214 and BEIR V estimates are based on the U.S. population of all ages, and the UNSCEAR 88 estimates are based on the population of Japan.

^c Unlike estimates from other reports, BEIR V estimates do not include radiation-induced cancer deaths in persons who would have died of cancer later.

^d These estimates apply to the entire population, and are one-half the risks for females.

^e These estimates were based on age-specific risk coefficients. The UNSCEAR estimates not in parentheses are based on constant (age-averaged) risk coefficients.

Table 3.18

Linear lifetime risk estimates^a for fatal cancer in persons exposed under age 20. Excess deaths per 10⁴ person-Gy

Type of cancer	NUREG/CR-4214 with modifications recommended in Section 3.5			BEIR V ^b
	Lower bound	Central	Upper bound	
Leukemia	111	111	111	184 ^c
All cancers except leukemia	556	1642	2088	1288
Breast ^d	63	114	163	106
Lung	88	265	662	47
Gastrointestinal	216	649	649	510
Other	189	614	614	625
Total	667	1753	2199	1472

^a This table is presented for the purpose of comparing linear risk estimates, without consideration of modification by dose and dose rate reduction factors. For this reason, estimates have not been modified to account for low doses and dose rates. Thus, the NUREG/CR-4214 central estimates for most cancers in this table are a factor of 2 higher, the NUREG/CR-4214 lower bounds are a factor of 4 higher, and the BEIR V estimate for leukemia is a factor of 2 higher than modified estimates would be.

^b Unlike estimates from other reports, BEIR V estimates do not include radiation-induced cancer deaths in persons who would have died of cancer later, and would be about 25% higher had these deaths been included.

^c This is the linear estimate, and is double the linear-quadratic estimate provided by BEIR V for low doses and dose-rates.

^d These estimates apply to the entire population, and are one-half the risks for females.

Table 3.19 (revised Table 3.1, NUREG/CR-4214)

Summary of the model used to determine upper bound, central, and lower bound lifetime risk estimate for mortality and incidence^{a,b}

Effect	Risk estimate		
	Upper bound	Central	Lower bound
Cancers due to other than <i>in utero</i> exposure			
Leukemia and bone	Use absolute linear estimate	Modify upper bound by a DDREF of 2 as indicated in Section 3.5.1	Modify upper bound by a DDREF of 4 as indicated in Section 3.5.1
Breast	Use age-specific relative linear estimate	Use alternative age-specific relative linear estimate	Modify absolute linear estimate by a DDREF of 4 as indicated in Section 3.5.1
Lung	Use age-specific relative linear estimate	Modify alternative age-specific relative linear estimate by a DDREF of 2 as indicated in Section 3.5.1	Modify absolute linear estimate by a DDREF of 4 as indicated in Section 3.5.1
Gastrointestinal	Use age-specific relative linear estimate	Modify age-specific relative linear estimate by a DDREF of 2 as indicated in Section 3.5.1	Modify absolute linear estimate by a DDREF of 4 as indicated in Section 3.5.1
Thyroid ^c	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate	Use age-specific absolute linear estimate
Skin	Use relative linear estimate	Modify upper bound by a DDREF of 2 as indicated in Section 3.5.1	Modify upper bound by a DDREF of 4 as indicated in Section 3.5.1
Other cancers	Use age-specific relative linear estimate	Modify age-specific relative linear estimate by a DDREF of 2 as indicated in Section 3.5.1	Modify absolute linear estimate by a DDREF of 4 as indicated in Section 3.5.1
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 <i>in utero</i> exposure	Use absolute linear estimate	Use absolute linear estimate multiplied by 0.4	Use absolute linear estimate multiplied by 0.4

^a The linear estimates referred to are given in Table 3.20 (mortality) and Table 3.21 (incidence).

^b For convenience, "linear lifetime risk estimates based on the absolute (relative) risk model" are referred to as "absolute (relative) linear estimates."

^c ¹³¹I is assumed to be as effective as external radiation for the upper bound thyroid cancer risk estimate, one third as effective for the central estimate, and one tenth as effective for the lower bound.

^d ¹³¹I is assumed to be as effective as external radiation for the upper bound thyroid nodules risk estimate, and one fifth as effective for the central estimate and lower bound.

Table 3.20 (revised Table 3.2, NUREG/CR-4214)

Risk coefficients and lifetime risk estimates for mortality from several cancer types

Effect	Period at risk (yrs)	Risk coefficient		Number of deaths ^a (per 10 ⁴ person-Gy)		Years of life lost ^a (per 10 ⁴ person-Gy)	
		Absolute (per 10 ⁴ PYGy)	Relative (per Gy)	Absolute	Relative	Absolute	Relative
Leukemia	2-27	4.5	--	97	--	3,379	--
<i>In utero</i> ^b	0-12	25 ^f	--	38	--	200	--
Bone cancer	2-27	0.4	--	9	--	300	--
Breast cancer							
Age-specific ^h	10-life	--	1.0 ^d ,0.4 ^d	--	84 ^e	--	1,400 ^e
Alternative age-specific ⁱ	10-life	--	0.7 ^d ,0.3 ^d ,0.1 ^d	--	54 ^e	--	930 ^e
Non-age-specific	10-life	2.6	--	43 ^e	--	973 ^e	--
Lung cancer							
Age-specific ^h	10-life	--	1.5 ^d ,0.5 ^d	--	331	--	4,875
Alternative age-specific ⁱ	10-life	--	0.6 ^d ,0.3 ^d	--	155	--	2,262
Non-age-specific	10-life	2.5	--	67	--	1,249	--
GI cancer							
Age-specific	10-life	--	1.2 ^d ,0.4 ^d	--	336	--	4,054
Non-age-specific	10-life	4.0	--	135	--	3,293	--
Thyroid cancer ^c	5-life	0.25 ^d ,0.12 ^d	--	7	--	203	--

Table 3.20 Cont. (revised Table 3.2, NUREG/CR-4214)

Risk coefficients and lifetime risk estimates for mortality from several cancer types

Effect	Period at risk (yrs)	Risk coefficient		Number of deaths ^a (per 10 ⁴ person-Gy)		Years of life lost ^a (per 10 ⁴ person-Gy)	
		Absolute (per 10 ⁴ PYGy)	Relative (per Gy)	Absolute	Relative	Absolute	Relative
Other cancer							
Age-specific	10-life	--	1.1 ^d ,0.25 ^d	--	276	--	3,847
Non-age-specific	10-life	3.5	--	118	--	2,882	--
<i>In utero</i> ^b	0-12	28 ^f	--	38	--	200	--

^a These risks are based on a linear model and in most cases must be modified as indicated in Table 3.19 to obtain central and lower estimates.

^b These estimates may be too high because of recent improvements in cure rates. See Section 3.3.3 of NUREG/CR-4214.

^c Thyroid cancer mortality risk coefficients have been obtained by reducing the incidence coefficients given in Table 3.21 by a factor of ten. See Section 3.3.3 and 2.6 of NUREG/CR-4214.

^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. For breast cancer, the three coefficients are for those exposed under age 20, 20-39, and ages 40 and over.

^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.

^h These age-specific estimates are used to obtain upper bound estimates.

ⁱ These alternative age-specific estimates are used to obtain central estimates.

Table 3.21 (revised Table 3.3, NUREG/CR-4214)

Risk coefficients and lifetime risk estimates for incidence of several cancer types

Effect	Period at risk (yrs)	Risk coefficient		Number of cases ^a (per 10 ⁴ person-Gy)		Years With cancer (per 10 ⁴ person-Gy)	
		Absolute (per 10 ⁴ PYGy)	Relative (per Gy)	Absolute	Relative	Absolute	Relative
Breast cancer							
Age-specific ^d	10-life	--	1.0 ^b , 0.4 ^b	--	245 ^c	--	3,092 ^c
Alternative age-specific ^e	10-life	--	0.7 ^b , 0.3 ^b , 0.1	--	159 ^c	--	2,084 ^c
Non-age-specific	10-life	7.4	--	122 ^c	--	1,796 ^c	--
Lung cancer							
Age-specific ^d	10-life	--	1.5 ^b , 0.5 ^b	--	369	--	677
Alternative age-specific ^e	10-life	--	0.6 ^b , 0.3 ^b	--	173	--	310
Non-age-specific	10-life	2.7	--	72	--	99	--
GI cancer							
Age-specific	10-life	--	1.2 ^b , 0.4 ^b	--	575	--	3,218
Non-age-specific	10-life	6.8	--	229	--	2,306	--
Thyroid cancer	5-life	2.5 ^b , 1.25 ^b	--	72	--	1,823	--
Skin cancer	10-life	6.7	0.5	226	888	--	--
Other cancer							
Age-specific	10-life	--	1.1 ^b , 0.25 ^b	--	552	--	4,994
Non-age-specific	10-life	6.8	--	229	--	2,717	--
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 indicated in Table 3.19 to obtain central and lower estimates.

^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. For breast cancer, the three coefficients are for those exposures under age 20, 20-39, and ages 40 and over.

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

^d These age-specific estimates are used to obtain upper bound estimates.

^e These alternative age-specific estimates are used to obtain central estimates.

Table 3.22 (revised Table 3.5, NUREG/CR-4214)

Central, upper, and lower estimates for lifetime risks of mortality resulting from low-LET exposure received at low doses (<0.2 Gy) or low dose rates (<0.1 Gy per hour)

Effect	Number of deaths (per 10 ⁴ person-Gy)			Years of life lost (per 10 ⁴ person-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 <i>in utero</i> exposure						
Leukemia	24	49	97	845	1,690	3,379
Bone	2.3	4.5	9	75	150	300
Breast	11	54	84	243	930	1,400
Lung	17	78	331	312	1131	4,875
Gastrointestinal	34	168	336	823	2,027	4,054
Thyroid	7.2	7.2	7.2	203	203	203
Other	30	138	276	721	1,924	3,847
Total ^e	126	499	1,140	3,222	8,055	18,058
Cancers due to <i>in utero</i> exposure						
Leukemia	1.2 ^f	1.2 ^f	3.0	80 ^f	80 ^f	200
Other	1.2 ^f	1.2 ^f	3.0	80 ^f	80 ^f	200

^a With the exception of thyroid cancer and cancers resulting from *in utero* exposure, these estimates are obtained by modifying the absolute linear estimates in Table 3.20 by a DDREF of 4.

^b With the exception of breast cancer, thyroid cancer and cancers resulting from *in utero* exposure, these estimates are obtained by modifying linear estimates in Table 3.20 by a DDREF of 2.

^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 These are the totals that would be obtained if all organs received the same dose.

^f These estimates are obtained by modifying the upper bound estimates by 0.4 (see Section 3.4.9 of NUREG/CR-4214).

4.0 GENETIC EFFECTS

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4.1 Introduction

Several Committees have published new genetic effects estimates since the NUREG/CR-4214 report appeared originally (NRC, 1985) and in revised form (NRC, 1989). The UNSCEAR published new estimates in UNSCEAR 86 that were different from those in its 1982 report (UNSCEAR, 1982) largely in that no estimates were made for congenital anomalies or other multifactorial diseases. UNSCEAR 88 does not make new genetic effects estimates per se. The BEIR V report makes new genetic effects estimates that differ in several respects from those of the earlier BEIR III report. Probably most important, the BEIR V Committee also declined to make estimates for the multifactorial diseases ("disorders of complex etiology") other than congenital anomalies, but elected to make new estimates for the category congenital anomalies by itself. This category had been included in the irregularly inherited class in both BEIR III and the 1982 UNSCEAR report. The ICRP, in its Publication 60, has revised its recommendations on radiation protection which includes hereditary effects estimates (ICRP, 1991). Single estimates are given for all serious effects, both excluding and including multifactorial effects, and a separate estimate of the multifactorial component "weighted for severity" is provided.

The main purpose of this document is to provide an update of the NUREG/CR-4214 genetic effects risk models in the light of the UNSCEAR 86, UNSCEAR 88, BEIR V, and ICRP 60 reports. It is our intention that this update serve only as a supplement to the more extensive review of the task of estimating the genetically related ill health that might be expected as a result of human radiation exposure during and after a nuclear reactor accident. We have accordingly not attempted to re-review the background material in depth in the present document; for this reader is referred to NUREG/CR-4214. However, we have taken advantage of the opportunity the present document provides to review additional material that has appeared in the literature or otherwise come to our attention during the past few years that is pertinent to several aspects of human genetic effects estimation. This new material is presented in Appendices to this section.

4.2 Chronic Low-LET Radiation Exposure

In Table 4.1 of NUREG/CR-4214, numerical risk estimates for five classes of genetic disorder are provided. It is convenient to consider each separately. However, ICRP 60 does not distinguish the different classes of effect for serious genetic effects except for multifactorial, and thus different comparisons with NUREG/CR-4214 are necessary. Table 4.1 compares BEIR V estimates with those recommended below in the same manner as did Table 4.1 of NUREG/CR-4214 with the BEIR III estimates.

4.2.1 Autosomal Dominants

Based essentially upon the BEIR III ranges of possible magnitude of effect for autosomal dominants and X-linked recessives, plus an estimate of the contribution of each to the totals, NUREG/CR-4214 made a central

Table 4.1 (revised Table 4.1, NUREG/CR-4214 Rev 1)

Numbers of naturally occurring and radiation-induced genetic disorders in a population of one million, according to the BEIR V report analysis and according to the present analysis. Assumes a 0.01 Gy dose

Type of disorder	Normal ^a incidence	BEIR V report ^b		This study (central estimates) ^c	
		First generation	All generations ^d	First generation ^e	All generations
Single-gene					
Dominant	4,800	7	48	15	70
X-linked	190	<1	<2	4	20
Chromosome aberrations					
Aneuploidy	1,830	<1	<1	4	5
Unbalanced translocations	290	<3	*V.L.I.* ^f	6	8
Congenital abnormalities	11,800	14	30	-- ^g	15
Totals ^h	18,900	25	80	30	120
Periimplantation wastage	260,000	--	--	230	240

^a For a total population of 10⁶ persons (16,000 live births per year) for 30 years (480,000 live births). New estimates based upon new estimates of normal incidence from BEIR V.

^b Cases expected in each generation of children from a population of 10⁶ persons each receiving a dose of 0.01 Gy. Assumes 30 year intergenerational interval and birthrate of 16,000 per year per 10⁶ persons, or 480,000 children per generation.

^c Calculated using the computer program described in Appendix 4G of NUREG/CR-4214, based on 1978 demography, which assumes a projected birthrate (births/year) of 16,000 for each of the first 30 years, 15,600 for each of the years 30 through 59, and 15,000 for years 60 through 89. The single value is the geometric mean of the range of values presented in the text of that report. Value for Congenital Abnormalities derived from BEIR V.

^d Based on doubling dose of 1.0 Gy, chronically delivered. Actually the BEIR V 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 Estimated directly from measured phenotypic damage or from observed cytogenetic effects.

^f Very little increase.

^g Any expressed in the first generation are already accounted for as single-gene dominants.

^h Totals rounded to avoid undue implying great precision.

estimate of 15 dominant effects in the first generation (for the 480,000 live births expected per million of parental population each exposed to 0.01 Gy) and 70 such effects over all generations. The UNSCEAR 86 estimates, corrected to the same basis and assuming that one-sixth of the combined total are X-linked, were about 6 in the first generation and about 36 over all generations. The BEIR V estimates, again corrected to the same basis, are essentially the same as the NUREG/CR-4214 estimates, even though arrived at in a somewhat different manner, and not really substantially different from the UNSCEAR 86 estimates. Thus, no revision of the NUREG/CR-4214 risk coefficient is recommended.

We note, however, that in contrast with BEIR III and the 1986 (and earlier) UNSCEAR reports, the authors of BEIR V chose to rely mainly on the "indirect" method of estimating first generation effects of dominant mutations by back-extrapolation from equilibrium estimates based upon doubling dose calculations, instead of the more "direct" method based upon actual observations of first generation effects. While as already noted above, this has made little difference in their estimates for first generation dominant effects, we are concerned that future research might yield data that would lead to substantial changes in numerical estimates depending on which method of estimation was used. In general, we believe that the "direct" method involves fewer uncertainties than the "indirect", and is thus preferable.

4.2.2 X-linked

The NUREG/CR-4214 central estimates were 4 cases in the first generation and 20 in all generations; the corresponding UNSCEAR 86 estimates are about 1 and 12, and those from BEIR V are about 1 and 2. Again, no revision of the NUREG/CR-4214 risk coefficient seems required.

4.2.3 Aneuploidy

Prior to NUREG/CR-4214, the BEAR and BEIR Committees and UNSCEAR had made no numerical estimates for this class of genetic effect, believing the evidence too weak to support the idea that there would be significant induction of this class of genetic effect among the offspring of irradiated populations. Setting a precedent, NUREG/CR-4214 estimated that there might be as many as 4 cases among the first generation offspring of one million persons exposed to 0.01 Gy, and possibly 5 over all generations. The UNSCEAR 86 (and UNSCEAR 88) continued to reject a numerical estimate, stating that any increase would be "probably very small". BEIR V, on the other hand, does give an estimate, though of " <1 ". It is recommended that the NUREG/CR-4214 estimates be retained unchanged.

Awa *et al.* (1988) in their cytogenetic study of the F₁ children of the A-bomb survivors found no significant increase in the frequency of sex chromosome trisomies (19 cases out of 8322 subjects from the exposed cohort and 24 cases among 7976 studied from the unexposed cohort). The sex chromosome trisomies should not have been at any selective disadvantage. The mean parental gametic dose to the exposed population was estimated to be 0.3 Sv. This lack of a significant increase is, however, not surprising, since extrapolation from the NUREG/CR-4214 estimate would predict at most one additional sex chromosome trisomy in the exposed group. (See also discussion in Appendix 4B).

4.2.4 Unbalanced Translocations

The UNSCEAR 86 estimates, corrected to a dose of 0.01 Sv, and the same population basis as used in NUREG/CR-4214, are 12 in the first generation and 19 over all generations. The corresponding BEIR V estimates are <3 and "very little increase". NUREG/CR-4214 estimated there would be 6 in the first generation and 8 in all future generations. It appears that the basic difference between the BEIR V and the NUREG/CR-4214 estimates, as was the case for the BEIR III estimate as well, continues to be the calculation in NUREG/CR-4214 of a specific oocyte translocation induction rate. There seems to be no reason to change the NUREG/CR-4214 estimate for unbalanced translocation.

It should be noted, however, that NUREG/CR-4214, BEIR V and the UNSCEAR reports base their unbalanced translocation risk estimates on comparisons of human and marmoset studies of spermatocytes derived from irradiated spermatogonia. The analyses estimate the proportion of aberrations that will be successfully transmitted to the next generation, using appropriate dose rate reduction and viability factors to derive their estimates. Each analysis also provides an estimate of the frequency of both balanced and unbalanced translocations types transmitted to the next generation. What is of interest is that the frequencies of balanced translocations predicted by these analyses are at least an order of magnitude larger than that actually observed cytologically in the offspring of the A-bomb survivors (Awa *et al.*, 1988). In the Japanese study, only one newly arisen balanced translocation was found in the nearly 8000 F₁ offspring of exposed parents (estimated mean parental generation dose was 0.3 Sv), and one case was also observed in approximately the same number of F₁ offspring from unexposed parents. Since balanced translocations are not expected to be selected against by reduced viability, these results, based on different methods of analysis, suggest that considerable uncertainty exists in the risk estimates. Ongoing studies of sperm from human males exposed to therapeutic doses of irradiation (derived from irradiated spermatogonia) used to fertilize hamster oocytes may provide more definitive information on this question.

4.2.5 Irregularly Inherited

There are very large differences in the way this class of genetically related ill health was handled in the three reports. While NUREG/CR-4214, following the earlier precedents, made a numerical estimate of 70 cases over all generations (any first generation effect was included in the dominant class), both the UNSCEAR 86 and BEIR V, in the light of recent information, declined to make any estimate at all. However, BEIR V did "break out" the subcategory of congenital abnormalities with origins other than chromosomal aneuploidy, and made estimates for this class of genetic effect (see below). Moreover, it is critical to note for this discussion that whereas BEIR III assumed a normal incidence of 43,200 of irregularly inherited diseases, the BEIR V Committee assumed about 576,000 diseases. Where BEIR III estimated there would be between 20 and 900 cases of irregularly inherited effects at equilibrium (i.e., over all generations in the case of an exposure of one generation only) for exposure of the parents of one million liveborn to one rem, BEIR V contains an estimate that there would be 10 congenital abnormalities in the first generation and between 10 and 100 at equilibrium. In fact, however, their first generation estimate of 10 cases is in error. The BEIR V Committee employed a mutational component of 0.35 in their calculation. However, the appropriate mutational component for dominants should have been 1.0, bringing the number of cases to 30 (The Chairman of the BEIR V Genetics

Subcommittee has agreed with our interpretation and this correction). NUREG/CR-4214, like BEIR III, made no separate first generation estimate for irregularly inherited effects (any such effects are included among the first generation dominant effects), and estimated there would be 70 over all generations.

The ICRP 60 report does estimate the multifactorial effects class (i.e., irregularly inherited) at $0.5 \times 10^{-2} \text{ Sv}^{-1}$ "weighted for severity", which may be compared with the NUREG/CR-4214 estimate of 70 effects over all time as a result of a single exposure of 1 million people to an individual dose of 0.01 Gy. Adjusting for the NUREG/CR-4214 population base, this ICRP estimate becomes 24 over all time, not a serious discrepancy.

In view of the BEIR V separate estimate of congenital abnormalities, it seems desirable to be able to break out this category from the NUREG/CR-4214 irregularly inherited effects estimate. BEIR V estimated a range, at equilibrium, of from 10 to 100 per million live births. The geometric mean is 32, which constitutes a central estimate. Adjusting for the NUREG/CR-4214 population base of 480,000 live births, this central estimate becomes 15 congenital abnormalities at equilibrium (i.e., over all time following exposure of a single generation), not including those already included with the first generation dominants, with range of from 5 to 48. However, any of these occurring in the first generation would be included in our first generation estimate for dominant effects, so we have not attempted to make a separate first generation estimate for congenital abnormalities in Table 4.1. To arrive at an estimate for all generations, we have simply adopted the BEIR V estimated range as already noted.

As stated earlier, both the recent BEIR V and the UNSCEAR reports have concluded that the irregularly inherited diseases make up a much larger component of the natural genetic disease incidence than they did in previous reports. BEIR V now includes the bulk of cardiovascular and neoplastic diseases as having some inherited contribution, though as yet of unknown magnitude. In their view, each member of the population will, on average, suffer more than one such multifactorial disorder during a lifetime. Accepting their estimate of 1.2 million such diseases per million liveborn, this converts to 576,000 natural incidence cases per 480,000 births for the population basis used in NUREG/CR-4214. This represents an enormous increase in the degree to which the BEIR committees believe genetic factors influence human ill health. The BEIR III estimate of 43,200 (using the NUREG/CR-4214 population basis), already a substantial increase over the BEIR I (NAS/NRC 1972), rises over an order of magnitude to 576,000. Unfortunately, as pointed out in BEIR V, "Most genes affecting the traits [disorders of complex etiology] are thought to have small effects, and new mutations would each contribute a virtually insignificant amount to the total susceptibility of the individuals who carry them". Indeed, it was "Because of great uncertainties in the mutational component of these traits and other complexities" that the BEIR V committee made no quantitative risk estimates for such traits, commenting "The risks may be negligibly small, or they may be as large or larger than the risks for all other traits combined".

Unfortunately, though the uncertainties are indeed great, we believe that it would be inappropriate to follow the BEIR V and UNSCEAR precedent and recommend abandoning any attempt to estimate quantitatively the numbers of irregularly inherited diseases that might result from a nuclear reactor accident using the NUREG/CR-4214 health effect models.

Current incidence estimates in BEIR V for disorders of complex etiology other than congenital abnormalities include three categories: heart disease, cancer, and (selected) others, representing, respectively, one-half, one-quarter and one-quarter of the total. Applying the same methods that were used in NUREG/CR-4214, we may estimate the number of irregularly inherited disorders to be expected over all generations following exposure of a population of one million to a dose of 0.01 Gy to be about 900 as a central estimate (i.e., the 13+ increase in current incidence from BEIR III to BEIR V, times the NUREG/CR-4214 estimate of 70, less our new separate estimate of congenital abnormalities of 15). Of these, 225 each would be in the cancer and "selected other" categories, and 450 would be heart disease.

However, recent information on the role of genetic factors in carcinogenesis as well as the revised estimates of mutational component and of mean generational persistence from the BEIR V report allow a somewhat more sophisticated analysis, as described below, yielding estimates, the central values of which are given in Table 4.2. We recommend their use in the estimation of health effects to be expected as a consequence of a nuclear reactor accident, in addition to the estimate already given for congenital abnormalities, instead of the single estimate for irregularly inherited disorders given in NUREG/CR-4214. The considerations involved in the new estimates given in Table 4.2 are as follows.

In the usual consideration of recessively inherited genetic diseases, the affected individual must receive two recessive alleles, one from each parent, in order for the disease to become manifest. Such is the case for such diseases as sickle cell anemia, albinism, and phenylketonuria to name just a few examples.

However, we are now aware of a number of situations in which the transmission of a single recessive gene either from a heterozygous parent or a *de novo* germ cell mutation can result in a predisposition to disease, e.g., specific cancers and possibly other tissue-specific diseases including cardiovascular diseases. When an individual receives such a recessive gene at conception, then all of the cells of the body are heterozygous, containing both the mutant gene and a normal dominant gene from the other parent. Should the normal gene later be altered in any one of a number of ways by a somatic mutation, a certain proportion of the individual's somatic cells will no longer contain a functional normal gene. The individual's tissue can thus be mosaic for both normal and mutant cells. If a mutant cell is a stem cell, it may undergo clonal expansion, and may subsequently have selective advantage in cell growth over the normal cells. Considering that the spontaneous mutation rate for certain genes in somatic cells ranges from 10^{-3} - 10^{-6} per cell, and that a human being is comprised of over 10^{14} cells, it is a virtual certainty that some cells eventually will be homozygous mutant cells. In addition, other mechanisms are known in heterozygotes to lead to either homozygosity of mutant genes, or loss of the normal gene leading to hemizogosity for the mutant gene. Complete or partial chromosome loss, resulting either from missegregation at mitosis or from chromosome damage, occurs at frequencies of 10^{-3} - 10^{-4} in dividing cell populations. If a cell remains viable after such a loss, then the mutant phenotype is expressed. Genetic recombination between the homologous chromosomes can also lead to homozygous cell lines either doubly mutant or doubly normal.

In the case of inherited retinoblastoma, a mutant gene (whose normal allele functions as a tumor suppressor), when transmitted to the next generation has a high probability of becoming homozygous in one or more somatic cells of some tissues or organs. The homozygous mutant cell has lost its tumor suppressor capability, and such mosaic individuals have a high probability of malignancies in the eye, or other tissues. The rarer form of the disease results when the two-step mutational events occur in a somatic cell homozygous for both normal

Table 4.2

Genetic risk estimates for selected irregularly inherited diseases in a population of one million, based upon BEIR V estimate of normal incidence of all irregularly inherited diseases except for congenital anomalies. Assumes a 0.01 Gy dose

Type of disorder	Normal incidence ^b	BEIR V report		This study ^a (central estimates)	
		First generation	All generations	First generation	All generations
Cancer	144,000	--	--	7 ^c	190 ^c
Cardiovascular	288,000	--	--	18 ^d	375 ^d
Selected other	144,000	--	--	9 ^d	190 ^d
Totals ^e	576,000	--	--	35	760

^a We emphasize here, as well as in the text, the extremely tenuous nature of these numerical estimates in light of the very large uncertainties involved.

^b Assumes a population of 10⁶ persons of all ages will produce 480,000 offspring per generation (30 years).

^c Our estimate for first generation cancer effects is based upon the assumption that there are between 50 and 100 "tumor suppressor" genes that might be mutated. See text.

^d Assumes a mutational component of 0.13, the geometric mean of the BEIR V range of from 0.05-0.35. The time to genetic equilibrium is assumed to be between 10 and 50 generations.

^e Totals rounded to avoid impression of great precision.

alleles. In the inherited form of retinoblastoma, multiple tumor foci usually arise bilaterally (in eye tissue and in other tissues as secondary sites), and the onset is earlier than in the non-inherited form. In the non-inherited form a single tumor, arising later in life, is usually found.

In cases of arteriosclerosis, plaques of cells form the focus of the sclerotic tissue. There is evidence indicating that these plaques are derived from single mutant cell lines. While it may be that many of these cases are exclusively somatic in origin, some probably result from the heterozygous inheritance of a defective recessive gene, which preconditions the eventual occurrence of the homozygous state in some somatic cells in different tissues. While such mutant somatic cell lines may be necessary for the stages of development of a given disease, it appears that more often than not they are not sufficient; other genic or chromosomal mutations or extrinsic or intrinsic environmental changes may be required in such a mutant cell line before a clinically recognized condition is triggered. Thus, the disease is of a multifactorial nature, with preconceptual mutational events, and possibly other events interacting.

With this conceptual background in mind, we have calculated some numerical estimates of risk for the irregularly inherited diseases described in the recent BEIR V document. We have also extrapolated these estimates to the observations that exist for the children of the A-bomb survivors as a "sensitivity test" to determine if such predictions are within the range of risk actually observed.

As mentioned, our knowledge of the mechanism of cancer has increased markedly within the past 5 years. To date, there are about 50 dominant acting oncogenes known. None of these have been shown to be germinally transmitted, and current collective wisdom is that such mutants would probably cause zygotic-embryonic death because of unregulated cell proliferation. On the other hand, there are also "anti-oncogenes" (tumor suppressor genes), whose normal function is to regulate the oncogenes. Mutations to loss of suppression are recessive, and in several cases now known, for example retinoblastoma and the Li-Fraumeni syndrome, they are heritably transmitted. We assume that at a minimum there must be about 50 such tumor suppressor genes. In the case of the p53 gene, the mutant form of the tumor suppressor gene appears to result from a specific DNA codon change, which would be a very infrequent type of mutation among those induced by radiation, perhaps 3 orders of magnitude lower in frequency than the commonly induced DNA deletion types. Assuming, however, that most of these tumor suppressor genes can be mutated by high-energy ionizing radiations, we would expect that there might be as many as 5 germinally transmitted recessive mutants per million F_1 per 0.01 Sv. The calculation uses the mouse-specific locus rate of $10^{-7}/0.01$ Sv (50 genes \times 10^{-7} mutations \times 2 parents/0.01 Sv = 10^{-5} or about 5 cases per 480,000 F_1). Not every individual inheriting a mutant tumor suppressor gene will necessarily sustain all the subsequent somatic mutation and other steps leading to a clinical manifestation of cancer, but we assume that the majority will. On the other hand, there could be as many as perhaps 100 such suppressor genes. This is the derivation of the central estimate for first generation cancer in Table 4.2 of 7 cases of cancer.

A second way of estimating the risk of induction of cancer-predisposing germ cell mutations derives from the doubling dose method. It has been estimated that between 5-10% of all malignancies have a hereditary component (Otter, 1990; Vasen *et al.*, 1990). Thus, among 480,000 F_1 , there might be 144,000 malignancies expected spontaneously, of which only 5-10% (7,200 - 14,400) would have a hereditary component. Assuming

that the mutational component for the hereditary class of cancers is high, perhaps 0.85 or more, we estimate that an 0.01 Sv exposure of a population of one million would result in 70-140 cases of cancer among descendants over all time. The calculation is:

$$144,000 \text{ (normal incidence)} \times 0.01 \text{ Sv [0.05 - 0.10 (mutational component)]} = 70-140.$$

If the time to genetic equilibrium is 10 generations, the first generation expectation is 7-14 [(70-140) + 10]; if genetic equilibrium took 50 generations, the first generation expectation is 1-3 cases. This range (say, 1-14 cases) is in good agreement with the estimate of 7 cases given above using the "direct" method.

We have used data presented in Yoshimoto *et al.* (1988, 1990, in press) to determine what the above model would predict for the A-bomb survivors' children. Through 1985, there was no significant increase in cancers among the nearly 27,000 children of exposed parents with DS 86 dose estimates, as compared with their 40,692 controls. The oldest children were 39 at the time of the analysis, and there were 40 cancers observed in the exposed cohort and 75 in the non-exposed. There were 10,648 F₁ with an average parental dose of 0.02 Sv, 9864 F₁ with 0.12 Sv, approximately 3500 with 0.35 Sv, 2300 with 0.80 Sv and 600 with 1.90 Sv. Because the parental exposures were acute, we applied a "linear-quadratic" analysis to this population. The calculation is $(10^{-7}D + 10^{-9}D^2) \times 50 \text{ loci} \times 2 \text{ parents} \times \text{number of children} = 10-12$ additional cancers which might be observed over the lifetime of this cohort. Most of the cancers would probably occur during the latter part of the individuals' lives, but in any case, such an excess would be statistically undetected. In fact, this would likely be true even if there were twice as many genes of the tumor suppressor variety.

Since most of the cancer expression is expected to occur late in life, the heritable recessive mutations are expected to be transmitted to subsequent generations (reproduction usually precedes the onset of cancer; 80-90% of reproduction occurs before age 30). Only those germinally transmitted mutants acting early in life may be selectively eliminated from the population. Only about 1% of the cancer incidence in the U.S. population is observed in the under 20 age group. (See Table A.4, NRC, 1990).

Unfortunately, we have even fewer insights into the genetic mechanisms underlying the other irregularly inherited diseases enumerated by BEIR V, the cardiovascular and other selected diseases, nor any way of estimating the most probable mutational component to be applied. We thus treat them as we did previously, using, however, the narrower range in mutational component of 0.05 - 0.35 suggested in BEIR V for congenital disorders. This range yields a geometric mean value of 0.13. The estimates in Table 4.2 for cardiovascular and for the selected other irregularly inherited diseases were derived as follows. Equilibrium (i.e., over all time) estimates were calculated as spontaneous incidence x fraction of doubling dose x mutational component = number of causes over all generations. For example, 288,000 cardiovascular disorders x 0.01 x 0.13 (geometric mean of BEIR V range of 0.05-0.35) = 375 cases over all generations. To obtain first generation estimates we simply assumed that some 1/10 to 1/50 of this total would be expressed in the first generation. It should be noted that the adoption of a mutational component of 1.0 for first generation expressed irregularly inherited disorders, as we have argued in the case of the BEIR V estimate for congenital abnormalities expressed in the first generation, is not applicable here; these are not single locus effects, and any first generation expression inferred from the equilibrium estimates must be considered to arise in individuals already "predisposed" by inheriting other genes involved in their multifractional disorders, not because of a dominant mode of inheritance.

The F_1 studies of the A-bomb survivors do not at this time include any clinical surveillance program, relying mainly on mortality records or the tumor registry for cause of death. The majority of the irregularly inherited diseases are late-acting, and expression has not yet occurred. Those diseases that are not the major cause of death usually go unnoticed. We estimate that there could be about 55 additional cases of non-cancer diseases, assuming a mutation rate of 5.6×10^{-5} per 0.01 Sv (27 cases/480,000; see Table 4.2). This represents the α coefficient in the linear quadratic equation; the β coefficient would be 1/100 as large for the dose distribution shown in our cancer calculation.

4.2.6 All Effects Except Multifactorial

The ICRP 60 report estimates the risk factor for these effects to be $0.5 \times 10^{-2} \text{ Sv}^{-1}$, of which about 80% are due to dominant and X-linked mutations. Presumably, the other 20% would include aneuploidy and unbalanced translocations. ICRP 60 goes on to state that about 15% occur in each of the first two generations. Thus, this estimate amounts to $5 \times 10^{-3} \text{ Sv}^{-1}$ over all generations, with $7.5 \times 10^{-4} \text{ Sv}^{-1}$ in the first generation. Adjusting for a dose of 0.01 Gy and the NUREG/CR-4214 population base of 480,000 live births per generation, these estimates become 3.6 effects in the first generation and 24 over all generations. The corresponding NUREG/CR-4214 central estimates for dominant, X-linked, congenital abnormality, aneuploidy and unbalanced translocations total 30 in the first generation and 120 over all time. The latter estimates are much higher than those derived from the ICRP 60.

One reason for the difference is that the ICRP estimate used a mutational component of 0.05 instead of the 0.13 we adopted from the BEIR V report. Another is that ICRP used the UNSCEAR estimates of current incidence, which are a factor of 2 smaller than those developed in BEIR V and used for our calculations.

4.3 Acute Low-LET Radiation Exposures

Neither UNSCEAR 86, UNSCEAR 88 nor the BEIR V reports address explicitly the question of dose rate-effect curve shapes for mutation endpoints or make any genetic effects estimates for acute exposures. Because substantial acute exposures could occur in the case of a nuclear power plant accident, NUREG/CR-4214 provided estimates based upon quadratic (called "linear-quadratic") dose-effect curves for high dose-rate, large exposures for most genetic effects. As no substantial changes are recommended in the low dose rate estimates, except for the increase in the estimate for all irregularly inherited disease except congenital anomalies and inclusion of a separate estimate for congenital abnormalities, there appears to be no reason to change the high dose-rate estimation methods. Specifically, Tables 2.9 and 2.10 of Part I of NUREG/CR-4214 (NRC, 1990) give models for calculating central estimates of genetic effects that include the dose-squared component (which is dropped for doses received at low dose rate) in which it is assumed for all classes of effect that the contributions of the linear and the dose-squared terms are equal at a dose of 1 Gy. It is recommended that these models be retained, with the exception that the multifactorial class be considered not to include an estimate of the congenital abnormalities class which may be calculated separately, if desired.

4.4 Estimated Impact of Genetic Disease

Based upon estimates of the numbers of years of life lost or impaired as a consequence of major human genetic disorders introduced by the UNSCEAR in its 1982 report, NUREG/CR-4214 also derived such estimates (Table 3.4). Also, UNSCEAR 88 provides a basis for such an estimate for congenital abnormalities. Based upon a study of these conditions in Hungary, they estimate about 8 years of actual life lost and 62 years of impaired life. Assuming the 25% impairment assumed for irregularly inherited conditions in NUREG/CR-4214 for congenital abnormalities as well, we have 8 years lost + (62 years impaired x 25% impairment), or about 24 effective years of life lost. Multiplying this by the estimated 15 cases to be expected over all generations from a single exposure of 0.01 Gy to a population of one million persons (Table 4.1) yields an estimate of approximately 360 effective years of life lost.

4.5 Summary

With one exception, the irregularly-inherited diseases, the UNSCEAR 86 and BEIR V estimates of genetic effects are similar to those adopted by NUREG/CR-4214, and no changes are recommended. For irregularly-inherited diseases, UNSCEAR 86 and BEIR V declined to make numerical estimates, though the ICRP 60 report does. It is recommended that the NUREG/CR-4214 recommendation for this class of genetic effects be changed to include the new natural incidence estimates of irregularly inherited diseases and their corresponding estimates of induced cases for both the first generation and accumulated over all generations, recognizing, however, the great uncertainties associated with these estimates. It is also recommended that the class of congenital abnormalities be treated separately.

Appendix 4A

Oocyte Mutational Sensitivity

In NUREG/CR-4214, we recommended that, because of the lack of mutation response from irradiated immature mouse oocytes due to their exquisite sensitivity to cell killing, mouse immature oocyte not be used as a basis for human risk estimates. Dobson and Felton (1983) provided evidence that the plasma membrane and not the nucleus was the target for this unique sensitivity. Straume *et al.* (1991) have now demonstrated that monoenergetic 0.43 MeV neutron can irradiate the mouse immature oocyte nucleus while simultaneously sparing the membrane from lethal damage. They could demonstrate that the dose-response relationship for chromosome aberrations in these immature oocytes was not significantly different from that in maturing oocytes. Griffin and Tease (1988), using very protracted gamma ray exposures, also demonstrated the induction of numerical and structural rearrangements in immature mouse oocytes.

These two studies, plus the fact that human immature oocytes are relatively radioresistant, strengthen the rationale for our previous risk estimates for the female and reduce the uncertainties in our lower estimates of risk by eliminating the mouse-derived zero values for mutational and chromosome damage.

Appendix 4B

Aneuploidy Induction

Two recent experiments have been used by Abrahamson *et al.* (1989, 1990) to estimate the induction rates of aneuploidy. The experiment by Griffin and Tease (1988) showed that low dose rate gamma irradiation applied to immature mouse oocytes increased the frequency of both chromosome aberrations and hyperdiploid cells scored in superovulated metaphase II cells. Martin *et al.* (1980) also demonstrated the presence of increased hyperdiploidy in human sperm cells, derived from spermatogonial cells exposed to therapeutic irradiation several years earlier. The sperm cells were subsequently used to fertilize hamster oocytes in order to examine the frequencies of induced abnormalities, both numerical and structural. The dose-related frequency of hyperdiploid cells was used to estimate the probability of producing viable aneuploid progeny. The RERF note by Abrahamson *et al.* (1989, 1990) estimated that a parental dose of 0.01 Sv could produce 9 cases of viable trisomies per 10^6 liveborn, a value in remarkably close agreement with the 4 cases per 480,000 arrived at in the NUREG/CR-4214 report using different assumptions.

Appendix 4C

Hiroshima-Nagasaki Studies

In 1990 Neel *et al.* reviewed, utilizing the new dosimetry system DS 86, the genetics data accumulated over the past 40 years, with the aim of establishing estimates of the doubling doses for humans. It should be noted that none of the endpoints studied are statistically significantly increased in frequency by irradiation. The minimum pooled doubling dose at the 95% probability level for three different endpoints was computed by them to be between 0.63 - 1.04 Sv. The mean conjoint parental doses for these subcohorts was approximately 0.4 Sv (0.36 for untoward pregnancy outcome, 0.4 for F₁ mortality and for F₁ cancer). The mean parental generation exposure is then approximately 0.2 Sv, indicating that for the majority of the F₁, their parental doses were quite low, and thus quite unlikely to have involved any two-track, dose-squared contribution. In their analysis, Neel *et al.* suggest adjusting the data by a factor of 2 for low-dose-rate situations, which would make their doubling dose estimate (lower 95% values) 1.26 - 2.08 Sv, which is up to a factor of two larger than the 1 Sv estimate utilized in NUREG/CR-4214 for the calculations employed in estimating dominant genetic disorders. Considering, however, that the NUREG/CR-4214 analysis was based on well-defined mouse genetic endpoints and on accurately measured radiation doses, while the Hiroshima-Nagasaki survivor F₁ data are of less certain genetic origin, that the mutational contribution to each endpoint had to be estimated, and that the dose estimate error for the A-bomb survivors is in the range of 35-50%, we conclude that the differences in these estimates do not really represent any serious disagreement.

In their attempt to produce a total human doubling dose, Neel *et al.* also included two other genetic endpoints. These were nucleotide base substitutions resulting in protein electrophoretic mobility variants of serum and red cell proteins, and sex chromosome trisomy. The minimum 95% confidence level of doubling dose Neel *et al.* derived for these two endpoints was 2.7 Sv for acute irradiation. However, whether radiation-induced germinal mutations have a substantial single base substitution component is still moot. The vast majority of radiation-induced germ cell mutations studied at the molecular level in *Drosophila* have been demonstrated to result from nucleotide deletions, ranging in size from a few nucleotides to beyond the limits of a single gene. A substantial proportion of radiation-induced mouse germinal mutations is known to be multiple locus deletions. Molecular analyses of the intragenic types in the mouse are presently underway. Thus, the estimation of doubling dose from protein mutations, which may well not include any substantial fraction of deletional mutations, may seriously overestimate the doubling dose for other mutational endpoints.

To estimate the total genetic doubling dose from their five genetic indicators, Neel *et al.* summed the individual regression coefficients, both positive and negative, and divided the estimated frequency of spontaneous mutations derived from the data by this value. In this manner, they estimate the overall doubling dose to lie between 1.7 Sv and 2.2 Sv for acute exposure. No "true confidence bounds" could be placed on this estimate. In their previous analyses (Schull *et al.*, 1981) the authors divided this estimate by two to obtain the gametic doubling dose value; they have since determined that this was an inappropriate procedure. Moreover, to estimate the doubling dose for the usual chronic or protracted exposures to which most populations are exposed, they multiplied the doubling doses by a factor of 2, deriving values of 3.4 Sv - 4.4 Sv, values that are considerably larger than the 1 Sv used in the previous UNSCEAR and BEIR reports, and in NUREG/CR-4214. However, in view of the many uncertainties involved, we believe it is proper to continue to utilize the 1 Sv value for risk estimation.

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11. ABSTRACT (200 words or less)

The Nuclear Regulatory Commission has sponsored several studies to identify and quantify the potential health effects of accidental releases of radionuclides from nuclear power plants. The most recent health effects models resulting from these efforts were published in two reports, NUREG/CR-4214, Rev. 1, Part I (1990) and Part II (1989). Several major health effects reports have been published recently that may impact the health effects models presented in these reports. This addendum to the Part II (1989) report, provides a review of the 1986 and 1988 reports by the United Nations Scientific Committee on the Effects of Atomic Radiation, the National Academy of Sciences/National Research Council BEIR V Committee report and Publication 60 of the International Commission on Radiological Protection as they relate to this report. The three main sections of this addendum discuss early occurring and continuing effects, late somatic effects, and genetic effects. The major changes to the NUREG/CR-4214 health effects models recommended in this addendum are for late somatic effects. These changes reflect recent changes in cancer risk factors that have come from longer followup and revised dosimetry in major studies like that on the Japanese A-bomb survivors. The results presented in this addendum should be used with the basic NUREG/CR-4214 reports listed above to obtain the most recent views on the potential health effects of radionuclides released accidentally from nuclear power plants.

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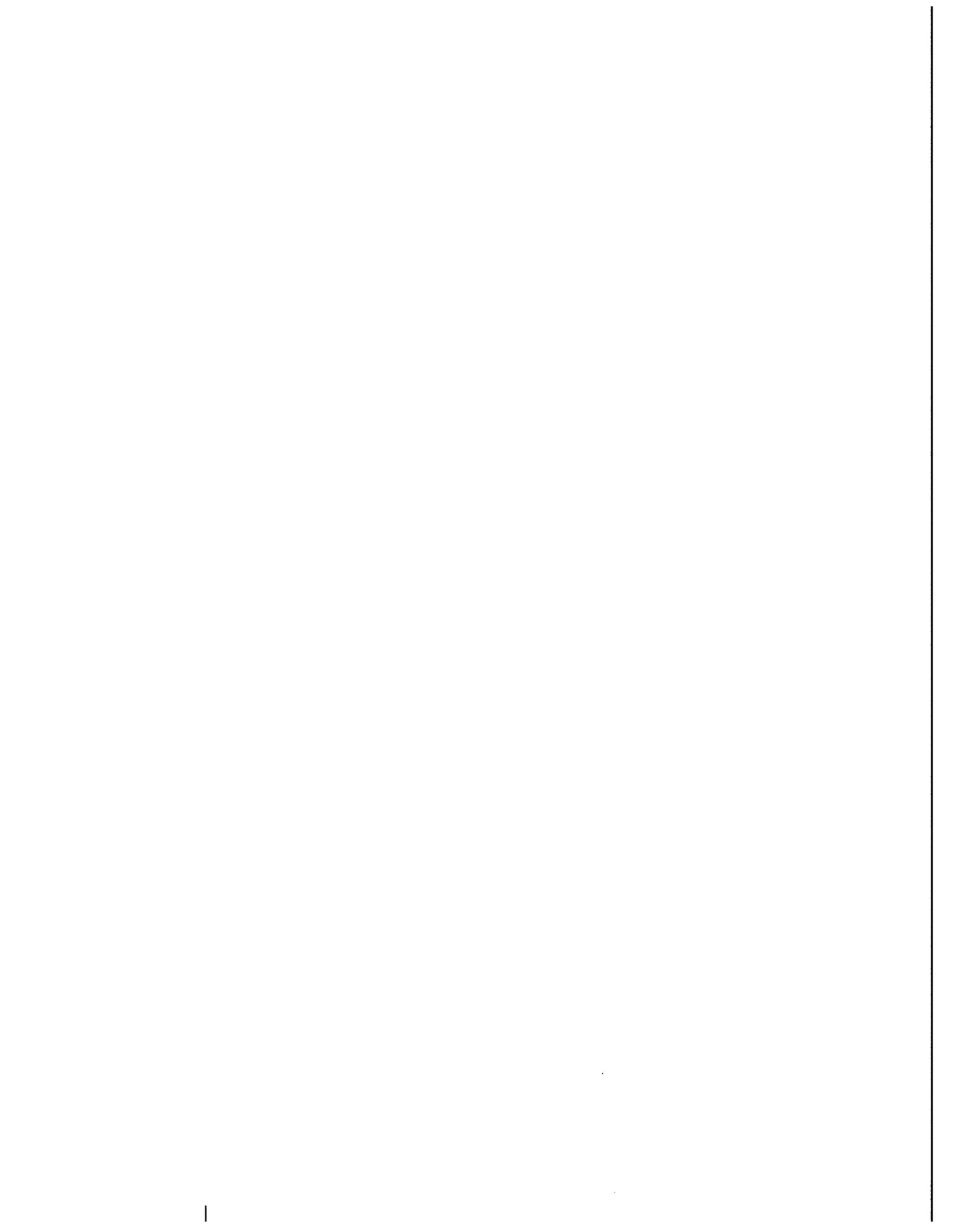
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